ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 30 (O.S., Vol. XXXIV) JANUARY, 1949 NUMBER 1

CONTENTS

	Page
Our Changing Viewpoint about Congestive Failure. Isaac Starr	1
Achlorhydria and Peptic Ulcer: A Further Study of the Rôle of Peptic Activity in the Pathogenesis and Course of Peptic Ulcer. William E. Ricketts, Walter Lincoln Palmer, Joseph B. Kirsner and Anna Hamann	24
Problems in the Natural History of Poliomyelitis. Albert B. Sabin	40
Androgen Therapy. W. O. Thompson	55
The Physiologic Effects of Physical Therapy. George Morris Piersol	69
The Use of the Anticoagulants in the Treatment of Diseases of the Heart and Blood Vessels. Irving S. Wright	80
Certain Clinical Aspects of the Application of Water Balance Principles to Heart and Kidney Disease. F. R. Schemm	92
Clinical Observations with Fagarine. D. Scherf, A. M. Silver and L. D. Weinberg	100
Xanthomatous Biliary Cirrhosis (A Clinical Syndrome). H. Edward MacMahon and S. J. Thannhauser	121
Case Reports:	
Q Fever: Report of a Case in Pennsylvania. O. Henry Janton, Amedeo Bondi, Jr. and M. Michael Sigel	180
Diffuse Melanosis, Pericardial Effusion, and Melanuria Associated with Malignant Melanoma: Case Report with Autopsy Findings. Norton D. Ritz	184
Transient Right Bundle Branch Block, Wide S-Wave Type, in Which Normal Conduction Occurred Both Spontaneously and in Response to Vagal Stimulation. Edward Nichols	196
Mediastinal Emphysema Following Anterior Perforation of a Gastric Ulcer. Dalton M. Welty	205
Disseminated Lupus Erythematosus with Pericardial Effusion. Arthur C. Curtis and S. F. Horne	209
Editorial—Recent Studies in Problems of Blood Coagulation	218
Reviews	223
College News Notes	227
New York as a Medical Center	239

Subscription per volume or per annum, net postpaid, $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $8.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph 4, section 538, P. L. & R., authorized October 7, 1936.

PUBLICATION JAN., 1949 NEW 5TH EDITION

DISEASES OF THE NOSE AND THROAT

(A Textbook for Students and Practitioners)

By

SIR ST. CLAIR THOMSON, M.D., F.R.C.P. Lond., F.R.C.S. England
and V. E. NEGUS, M. S. Lond., F.R.C.S., England

Consulting Surgeon for Diseases of the Throat, Nose and Ear, King's College Hospital; Hunterian Professor and Hunterian Bronze Medalist, Royal College of Surgeons of England; Corresponding Fellow, American Laryngological Association; Honorary Fellow, Amer. Laryngol., Oto. and Rhinol. Soc., and New York Laryngol. Soc., Corresponding Member American Bronchoesophagic Society; Past President, Section of Laryngology, Royal Society of Medicine.

FIRST REVISION SINCE 1937

This is the first revision since 1937 of an internationally famous text which gained its preeminent position by the clarity of its writing, its exhaustive coverage of the subject, the broad experience of its authorship, the stress placed on clinical and pathological bearings and on the natural methods of defense and repair which are so frequently overlooked.

Greater alterations have been made than in any previous editions. References to the literature have been reduced, More attention has been paid to such subjects as the complications of inflammatory processes and the general principles of defense against infection by chemotherapy and antibiotics. Many colleagues of Negus have reviewed and amended various sections in an attempt to secure accuracy and eliminate discrepancies. Many original illustrations have been replaced and many new figures contributed by such artists as Marchant, McClarty and Stewart.

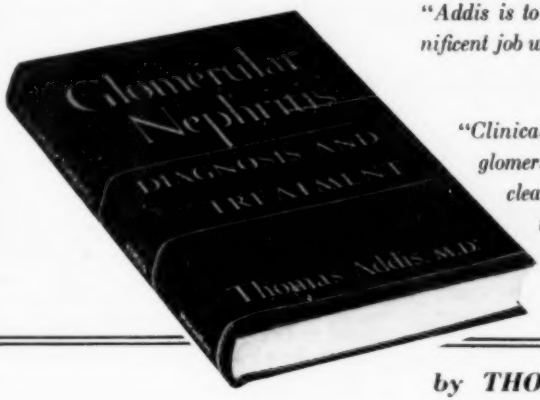
Rewritten or heavily revised subjects include: Malignant Disease of the Naso-Pharynx; Treatment by Sulfonamides, Penicillin, Radiotherapy and Vitamins; Allergy; Nasal Physiology (with ack. to Proetz); Acute Rhinitis; Sinus Infection in Children; Laryngeal Paralysis; Neurological Diseases of the Larynx; Congenital Laryngeal Stenosis; Inflammatory Diseases of the Lung; Acute Tracheo-bronchitis; Foreign Bodies and Peroral Endoscopy.

The descriptions of various operations have been shifted from the end of the book to the appropriate sections where they belong.

Probably no other modern work on diseases of the nose and throat is so highly regarded as a text for the specialist and graduate student.

990 Pages. 369 Figs. 13 Color Plates. 20 Radiographic and 11 other plates. 5th Edition. January, 1949. $16.00

APPLETON-CENTURY-CROFTS, INC.
35 West 32nd Street, New York 1, New York



"Addis is to be complimented on a magnificent job well done."

Gastroenterology

"Clinical and therapeutic problems of glomerular nephritis are discussed clearly, simply, and expertly in this monograph."

U. S. Quarterly Book List

by THOMAS ADDIS, M.D.

"The book is culturally a classic because of its descriptions, i.e. of the intimacy necessary between physician and the patients study, the description of the process of arriving at a diagnosis (as contrasted to the "scientific" method of looking at laboratory reports), of the philosophy of the care of the patient and because of the honesty that shines forth from every page. Here is no dogmatic preacher but a fellow physician trying to find the truth and trying to help you with your patients."

Clinical Medicine

"Actually the book contains much more than the title suggests. It serves as a medium for presenting not only Addis' often unorthodox views on Bright's disease, but also his basic philosophy of medical practice at a time when accumulation of knowledge in diverse fields has rendered it more difficult for the individual physician to insure his patient the maximum available help." . . . "This book is an important contribution which will reward the close attention of serious students of Bright's disease and should leave an imprint on thought and practice in the field."

Journal of the American Medical Association

338 pp. *Illus.* *$8.00*

THE MACMILLAN COMPANY

60 Fifth Ave., New York 11, N. Y.

Please send me ..... copies of GLOMERULAR NEPHRITIS @ $8.00.

NAME .....

ADDRESS .....

New (2nd) Edition — Just Ready

Soffer · Diseases of the Adrenals

By LOUIS J. SOFFER, M.D.

Associate Attending Physician, The Mount Sinai Hospital, New York City; Assistant Clinical Professor of Medicine, Columbia University.

The nature and manifestations of endocrine disorders and the diagnostic procedures which facilitate their early recognition are given clearly and concisely in this useful book. The thoroughly revised and enlarged *new (2nd) edition* contains virtually all of the recent knowledge concerning the adrenals and presents it clearly and concisely to clinicians and to students of endocrinology.

Dr. Soffer has incorporated new studies on the physiology of the adrenal glands, laboratory procedures for the diagnosis of adrenal cortical disease and new therapeutic measures in the treatment of Addisonian crisis and Cushing's syndrome.

Additional features of this well-balanced monograph include a detailed description of pathogenic symptomatology and laboratory findings in Addison's disease, the newer methods in the diagnosis of pheochromocytoma, an entire chapter on the adrenogenital syndrome and full consideration of the relationship of the adrenals to all other glands of internal secretion.

This comprehensive, well-written book offers the precise biochemical techniques that are so helpful in revealing the true nature of the functions of these glands and which enable us to understand the diseases associated with them.

New (2nd) Edition. 320 Pages. 45 Illustrations and 3 Plates in Color. $6.50.

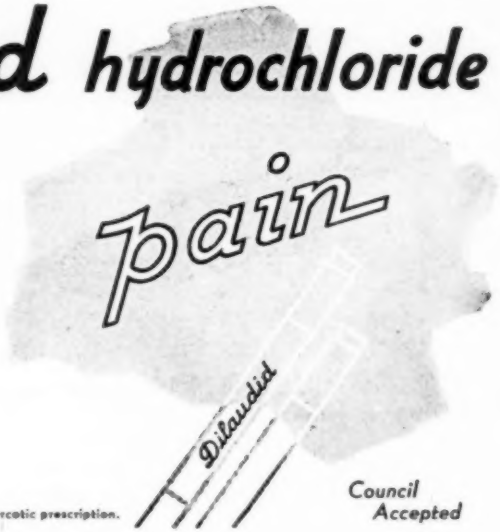
Washington Square **LEA & FEBIGER** Philadelphia 6, Pa.

Dilaudid hydrochloride

For pain in acute or hopelessly chronic conditions when an opiate is required, try Dilaudid hydrochloride for quick relief.

DOSE: 1/48 to 1/20 grain.

In hypodermic and oral tablets, rectal suppositories and powder.



Council Accepted

* Dilaudid HCl, dihydromorphinone HCl, requires a narcotic prescription.

BILHUBER-KNOLL CORP. ORANGE, NEW JERSEY

LIPPINCOTT SELECTED PROFESSIONAL BOOKS

New approaches to the science of diagnosis

Signs and Symptoms: Their Clinical Interpretation

Edited by CYRIL M. MACBRYDE, M.D., F.A.C.P., With 20 Contributing Authors

439 Pages.
74 Illustrations,
7 Color Plates.
$12.00

This standard text and reference on applied clinical pathological physiology and basic diagnostic processes is unique in its approach to understanding the manifestations of disease. It starts with the symptom and proceeds logically, as the practitioner must, toward the diagnosis. *"Here in concentrated form is graduate education of high quality. The illustrations are excellent and adequately supplement the text . . ."*—JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

Diagnosis in Daily Practice:

An Office Routine Based on the Incidence of Disease

By BENJAMIN V. WHITE, M.D. and CHARLES F. GESCHICKTER, M.D.

693 Pages.
360 Illustrations.
$15.00

Three essential steps in diagnosis are concisely presented in this book: how to elicit important signs, simplify the procedure of differential diagnosis and evaluate clinical findings through the use of pertinent data. A complete integration of the knowledge acquired in hospital training in diagnosis and its application to general practice. *"The authors are to be congratulated for . . . the practical selectivity with which they have combined the ideas and ideals of the pathologist and the clinician into such a splendid volume."*—THE CONNECTICUT STATE MEDICAL JOURNAL.

Lippincott Books Philadelphia London Montreal

J. B. LIPPINCOTT COMPANY, East Washington Square, Philadelphia 5, Pa..
Enter my order and send me: ☐ *MacBryde*, Signs & Symptoms, $12.00
☐ *White & Geschickter*, Diagnosis in Daily Practice, $15.00

Name ..... ☐ Cash enclosed
Address ..... ☐ Send C.O.D.
City, Zone, State ..... ☐ Charge my account

THOSE INDEFINITE SYMPTOMS . . .

Chronic fatigue, lassitude, general malaise, nausea, sleeplessness, headache, lost appetite—may be but the indications of derangement of the body's acid-base balance. Illness lowers the alkali reserve and acidosis decreases the effectiveness of many drugs.

Kalak (®)

A CARBONATED MULTI-BASE MINERAL WATER

replenishes the principal alkalies of which the reserve is composed. Its palatability makes it the easy answer to alkalization. It serves as a useful adjuvant in treatment when administration of the sulfonamides, penicillin, etc. is indicated and in the acid-alkali rotation method of therapy in urinary infections.

Kalak Water is available at all pharmacies.

KALAK WATER CO. OF NEW YORK, INC.
30 Rockefeller Plaza, New York 20, N. Y.

for Fifty Years

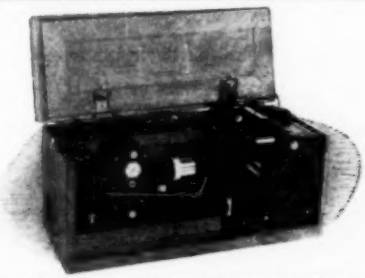
PROFESSIONAL PROTECTION

THE
MEDICAL PROTECTIVE COMPANY
FORT WAYNE, INDIANA

What you get in a CAMBRIDGE!

"My CAMBRIDGE and I started practice together."
"CAMBRIDGE Records are a must in referred cases."
"My CAMBRIDGE never lets me down."
"My CAMBRIDGE is time-tested."
"With a CAMBRIDGE accuracy is assured."
"My CAMBRIDGE gives me everything."

✓	*Fully Developed*	✓	*Acceptable Records*
✓	*Known Accuracy*	✓	*Long Life*
✓	*Dependability*	✓	*Proven Value*



The "Simpli-Trol" Portable Model is contained in one case, 8" x 10" x 19", and weighs only 30 lbs. Mobile and Research Models are also available. Line operation from any electric outlet eliminates battery nuisance. All models may be arranged to record heart sounds, pulse, and electrocardiogram simultaneously.

The present day Cambridge Electrocardiograph is the acme of simplicity and convenience. A CAMBRIDGE seems never to wear out. It is significant that today's SIMPLI-TROL Portable Model and the many thirty-year-old models that are still in daily operation, produce the same accurate records.

The CAMBRIDGE has always been accurate, and dependable. Each improvement has been fully developed before it was incorporated in the instrument. When you, Doctor, buy a CAMBRIDGE you know that it is not an experimental model but a tried and proven scientific instrument. *You can afford no less . . . nor can you buy more.*

Send for descriptive literature

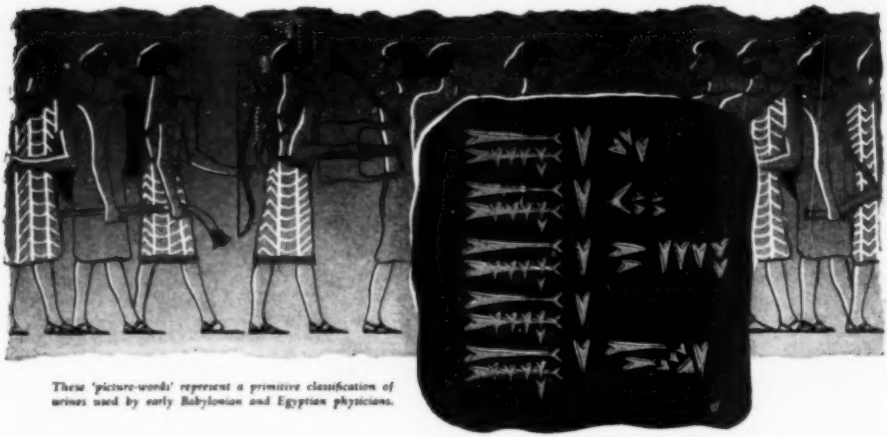
CAMBRIDGE INSTRUMENT CO., INC., 3715 Grand Central Terminal, New York 17

Pioneer Manufacturers of the Electrocardiograph

Chicago 12, 2400 W. Madison St. Philadelphia 4, 134 S. 36th St. Cleveland 15, 1720 Euclid Ave.

CAMBRIDGE ELECTROCARDIOGRAPH

AND THE CAMBRIDGE ELECTROKYMOGRAPH, PLETHYSMOGRAPH, AMPLIFYING STETHOSCOPE, RESEARCH pH METER, BLOOD PRESSURE RECORDER, LINDEMANN ELECTROMETER, ETC.



These 'picture-words' represent a primitive classification of urines used by early Babylonian and Egyptian physicians.

centuries to perfect seconds to perform

When Sumerian and Babylonian physicians, *circa* 4000 B.C., noted the varying colors and constitutions of the "water of the phallus," they were probably not the first uroscopists in history. They were assuredly not the last, for fifty-odd centuries were to elapse before Fehling's first paper on the copper reduction test for urine-sugar appeared in 1848.

But centuries to perfect diagnostic procedures are condensed into seconds to perform the reliable *Clinitest*® method for urine-sugar levels. From start to finish, the test takes less than a minute. This tablet method is simplicity itself . . . readily learned by every diabetic patient. External heating is uniquely eliminated by the *Clinitest* procedure. Routine test interpretation is made easy.

AMES

Clinitest

for urine-sugar analysis

AMES COMPANY, INC. • ELKHART, INDIANA

Medicine

lives the legend of Hercules

Contemporary Medicine accomplishes Herculean feats as a matter of daily routine . . .

In 1880, within the memory of many still living, a diphtheria epidemic in the city of Chicago exacted the terrible toll of 291 persons in each 100,000. Eleven years later in the same city, an outbreak of typhoid killed 172 in each 100,000.

By 1944, however, the diphtheria and typhoid death rates in Chicago had been reduced to *one* per *million* each.

Contemporary Medicine is a story of progress achieved through cooperative effort . . . a story of enlightened teamwork on the part of the clinician, the research worker, and Pharmacy, as exemplified in the modern pharmaceutical laboratory.

At Bristol Laboratories, we recognize the privilege of sharing in this cooperative effort. Success in discharging this trust is measured by the increasing thousands of physicians who specify Bristol.

HOW TO DO IT *without* MIRRORS

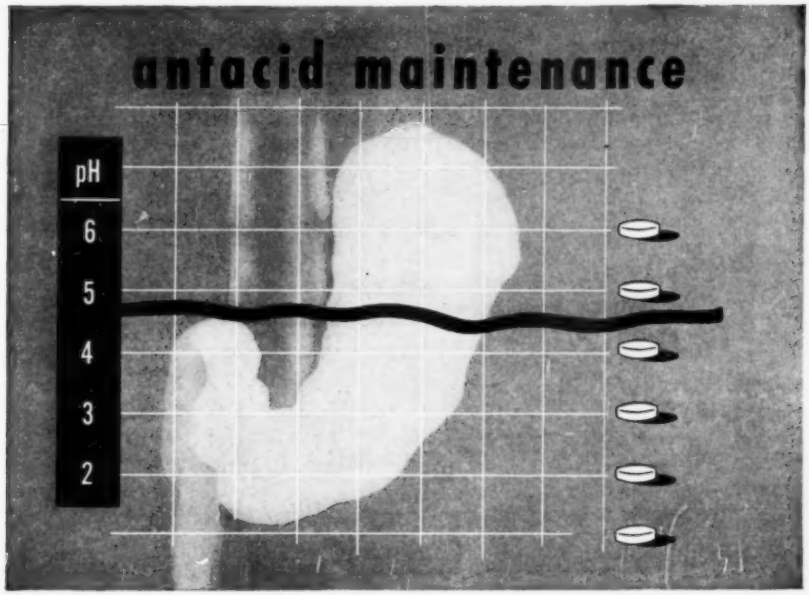
. . . WHEN PROLONGED DIETING BECOMES DULL

Of course she *wants* to be thinner, healthier and prettier, but sticking to the diet you prescribe may become very difficult after a time. When scales show she is cheating, you might prescribe Desoxyn Hydrochloride to depress the appetite. Desoxyn may be used until a satisfactory weight is obtained, or new eating habits definitely established. • When not contraindicated, Desoxyn provides a simple, safe and effective curb for the appetite, and further aids in the therapeutic reducing program by producing a feeling of well-being and a desire for greater activity. A 2.5 mg. tablet two or three times a day before meals is usually enough in a reducing schedule. • In addition to prescription use in obesity, Desoxyn may be given in a wide variety of conditions where a stimulant for the central nervous system is required. Clinical tests show its effectiveness in smaller doses, with quicker onset, longer effect, fewer side-effects.
For new literature, write to ABBOTT LABORATORIES, NORTH CHICAGO, ILLINOIS.

Desoxyn® *Hydrochloride*

(Methamphetamine Hydrochloride, Abbott)

TABLETS: *2.5 mg. and 5 mg.* **ELIXIR:** *20 mg. per fluidounce* **AMPOULES:** *20 mg. per cc.*



Healing of peptic ulcer must be followed by effective antacid maintenance therapy to prevent recurrence. This can be achieved conveniently with agreeable, easy-to-carry Creamalin Tablets and Capsules.

Through sustained reduction of gastric acidity without the danger of alkalosis, nonabsorbable Creamalin provides reliable and safe antacid control for the ambulatory ulcer patient.

FIRST BRAND OF ALUMINUM HYDROXIDE GEL

Creamalin®

TABLETS: Tins of 12, bottles of 50 and 200
CAPSULES: Boxes of 24, bottles of 100

CREAMALIN, trademark reg. U. S. & Canada

Winthrop-Stearns INC.
NEW YORK 13, N. Y. WINDSOR, ONT.

Widely prescribed

IN THE SEQUELAE OF EPIDEMIC ENCEPHALITIS

A THERAPY THAT EMBRACES IN THEIR NATIVE STATE THE ENTIRE ALKALOIDS OF STRAMONIUM

STRAMONIUM PILLS

(DAVIES, ROSE)

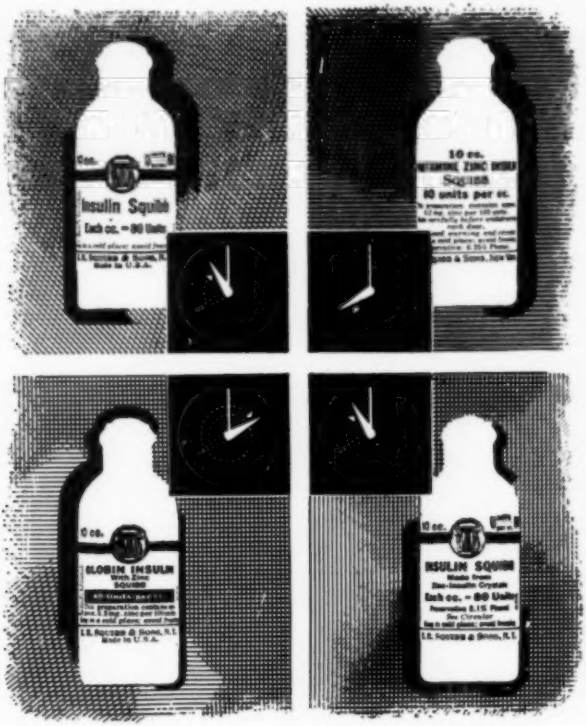
0.15 GRAM (APPROX. 2½ GRAINS)

These pills exhibit the powdered dried leaf and flowering top of Datura Stramonium, alkaloidally assayed and standardized, and therefore contain in each pill 0.375 mg. (1/170 grain) of the alkaloids of stramonium.

Sample for clinical test and literature mailed upon request

DAVIES, ROSE & COMPANY, LIMITED
Pharmaceutical Manufacturers
Boston 18, Mass., U. S. A.

St 3



4 forms for different requirements

The ever-increasing life-expectancy for diabetic patients is bringing ever-increasing need for purified, potent and uniform insulin.

Rigidly standardized, Squibb Insulin is available in four forms—for short, intermediate or long action—to meet the individual requirements of different diabetic patients.

INSULIN SQUIBB—10 cc. vials (40, 80 & 100 units per cc.)

PROTAMINE ZINC INSULIN SQUIBB
10 cc. vials (40 & 80 units per cc.)

GLOBIN INSULIN, WITH ZINC, SQUIBB
10 cc. vials (80 units per cc.)

INSULIN FROM ZINC INSULIN CRYSTALS SQUIBB
10 cc. vials (40 & 80 units per cc.)

INSULIN

SQUIBB

MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

The Long and Short of digitalis therapy!

With Digitaline Nativelle, cardiotonic influence usually becomes apparent within *three* hours. Full digitalization can be accomplished as rapidly as *six hours —instead of in days!*

Only such effectiveness brings the patient the desired, *quick relief* of air hunger and discomfort—and with virtual freedom from side effects. The physician will welcome the ease of administration as well as the considerably greater accuracy in therapy.

Simplicity of administration . . .

RAPID DIGITALIZATION . . . 1.2 mg. in equally divided doses of 0.6 mg. at three-hour intervals.

MAINTENANCE . . . 0.1 or 0.2 mg. daily depending upon patient's response.

CHANGE-OVER . . . 0.1 or 0.2 mg. of Digitaline Nativelle may advantageously replace present maintenance dosage of 0.1 gm. or 0.2 gm. of whole leaf.

Current references and comprehensive brochure "Management of the Failing Heart" available on request. Also, if you wish, we will send a full digitalizing dose. Simply address Research Division, Varick Pharmacal Company, 75 Varick Street, New York 13, N. Y.

Digitaline Nativelle

. . . active glycoside of digitalis purpurea (*digitoxin*)

changing from PZI to GLOBIN INSULIN

When protamine zinc insulin treatment is complicated by post-prandial hyperglycemia, nocturnal insulin reaction, protamine sensitivity, or other difficulties, a change to Globin Insulin often results in the desired improvement. The change is achieved in three steps:

1. THE INITIAL CHANGE-OVER DOSAGE: The first day, 30 minutes or more before breakfast, give a single dose of Globin Insulin, equal to ½ the total previous daily dose of protamine zinc insulin or of protamine zinc insulin combined with regular insulin. The next day, dose may be increased to ⅔ former total.

2. ADJUSTMENT TO 24-HOUR CONTROL: Gradually adjust the Globin Insulin dosage to provide 24-hour control as evidenced by a fasting blood sugar level of less than 150 mgm. or sugar-free urine in the fasting sample.

3. ADJUSTMENT OF DIET: Simultaneously adjust carbohydrate distribution of diet to balance insulin activity; initially 2/10, 4/10 and 4/10. Any midafternoon hypoglycemia may usually be offset by 10 to 20 grams carbohydrate at 3 to 4 p.m. Base final carbohydrate adjustment on fractional urinalyses.

Most mild and many moderately severe cases may be controlled by *one daily injection of 'Wellcome' Globin Insulin with Zinc.* Vials of 10 cc.; 40 and 80 units per cc. Developed in The Wellcome Research Laboratories, Tuckahoe, New York. U.S. Pat. 2,161,198. Literature on request.

'Wellcome' Trademark Registered

'WELLCOME' Globin Insulin WITH ZINC

BURROUGHS WELLCOME & CO. (U.S.A.) INC., 9 & 11 EAST 41ST STREET, NEW YORK 17, N.Y.

westsal
TRADE MARK

the only salt substitute that tastes exactly like salt

westsal is a joy to patients on low-salt (sodium) diets. It's the *only* salt substitute that makes food taste *exactly* as if seasoned with salt. No bitter, no disagreeable taste. Used freely at the table—in cooking and baking. ● Sodium-free, safe, convenient, *westsal* assures eating without cheating, a minimum intake of harmful sodium, better nourishment, and grateful, happier, patients in . . .

congestive heart failure • hypertension • toxemias of pregnancy

send for tasting samples

WESTWOOD PHARMACEUTICALS, Dept. AI ● 468 Dewitt St., Buffalo 13, N. Y.
division of Foster-Milburn Co.

westsal is a solution of lithium chloride with small amounts of citric acid and potassium iodide (iodizing traces). Bottles of 2¼ oz.

Solve the Protein Taste Problem with...

MERITENE tastes so good that patients really enjoy taking it. Just 3 ounces of MERITENE, mixed with milk, will provide over 50 extra grams of whole protein in your patient's daily diet. MERITENE is available in one-pound cans, plain or chocolate flavor, at only $1.65 per pound.

THE DIETENE COMPANY

518 FIFTH AVENUE SOUTH, MINNEAPOLIS 15, MINNESOTA

ACCEPTED COUNCIL ON FOODS AND NUTRITION AMERICAN MEDICAL ASSOCIATION

Not advertised to the laity . . .

THE DIETENE COMPANY DEPT. MI 19
518 FIFTH AVENUE SOUTH, MINNEAPOLIS 15, MINNESOTA

Please send me a free sample of MERITENE, the fortified whole-protein supplement, and descriptive literature.

Name..... M.D.
(Please Print)

Address.....

City.....Zone....State.....

Only

IN THE DIRECT-WRITING

VISO CARDIETTE

. . . WILL YOU BENEFIT BY THIS COMBINATION OF ELECTROCARDIOGRAPH ADVANTAGES . . .

Standard 'cardiograms
Assurance of accuracy
Modern, simplified design
A background of experience
Nationwide acceptance
Complete service by the maker

ACCEPTED COUNCIL ON PHYSICAL MEDICINE AMERICAN MEDICAL ASSOCIATION

SANBORN COMPANY
CAMBRIDGE 39, MASSACHUSETTS

Offices in New York, Philadelphia, Baltimore, Washington, Cleveland, Detroit, Chicago, Atlanta, Miami, New Orleans, Dallas, St. Louis, Minneapolis, Denver, Los Angeles, San Francisco, Seattle.

Natural antirachitic medication . . .

White's Cod Liver Oil Concentrate Liquid provides potent, antirachitic, natural vitamins A and D. Each two drops is equivalent, in vitamin content, to one teaspoonful of cod liver oil,* containing 312 units of vitamin D wholly derived from cod liver oil, and 3,120 units of vitamin A, supplied by cod liver oil concentrate adjusted and standardized with fish liver oils.

ECONOMICAL. Cost-to-patient—about a penny a day for antirachitic protection of average infant. In convenient, palatable Liquid form—dropper administration.

Also available in pleasant-tasting Tablets and higher potency Capsules. White Laboratories, Inc., Pharmaceutical Manufacturers, Newark 7, N. J.

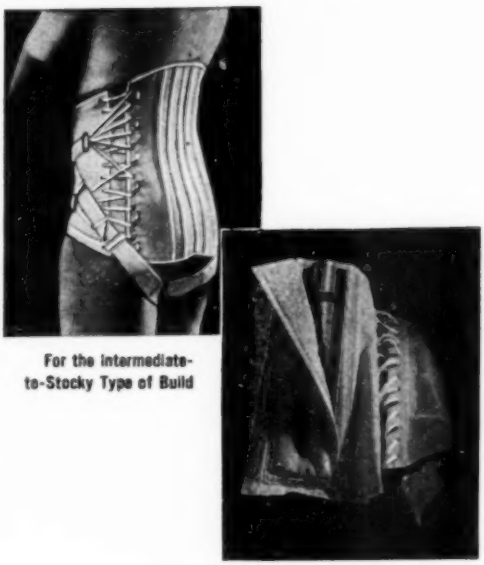
White's Cod Liver Oil Concentrate Liquid

One of White's Integrated Pediatric Vitamin Formulas

*U. S. P. Minimum Requirements

CAMP SUPPORTS *for the* LOW BACK

Discussing the general treatment of low back pain in a recent article, an orthopedic surgeon* comments on supports (among other items) as follows: "The second remedy tried by time is further rest provided by support after the patient gets out of bed. Various corsets, braces, and casts have been used and the one criterion is that they be well fitted and do the work intended."



For the Intermediate-to-Stocky Type of Build

The Camp lumbosacral support (illustrated) fits down over the gluteal region and restricts the motion of the pelvic and lumbar joints. The lower adjustment following about the major portion of the pelvic girdle is a prime factor in relieving the weight-bearing joints of the lower spine.

The support lends itself readily to reinforcement with the Camp spinal brace (illustrated). The brace is made of spring steel and comes in varying lengths – twelve, fourteen, sixteen, and eighteen inch lengths. Aluminum uprights and pads are also provided by Camp for reinforcement of orthopedic supports.

Camp fitters are trained and supervised by nurses and instructors.

*Hugh T. Jones, M.D.
Low Back Pain from the Orthopedic Standpoint
California Medicine
Vol. 68, February, 1948

S. H. CAMP and COMPANY • JACKSON, MICHIGAN

World's Largest Manufacturers of Scientific Supports

Offices in New York • Chicago • Windsor, Ontario • London, England

Clinically approved

Today, there is a wealth of clinical evidence supporting the use of Meonine as a supplement to the protein-rich diet usually prescribed for liver damage associated with malnutrition, pregnancy, allergy, certain chemical poisons, and alcoholism.

Typical of this evidence is a Beams-Endicott paper*. The authors reported that a methionine supplement seemed to cause regeneration of the liver parenchyma in cirrhotic patients, irrespective of the amount of protein and vitamins in the diet.

Complete bibliography on request. Meonine is supplied in 0.5 gram tablets. Wyeth, Phila., Pa.

*Beams, A. J., and Endicott, E. T., Histologic changes in the livers of patients with cirrhosis treated with methionine. Gastroenterology 9:718-735 (Dec.) 1947.

MEONINE®
for liver damage
(dl-Methionine Wyeth)

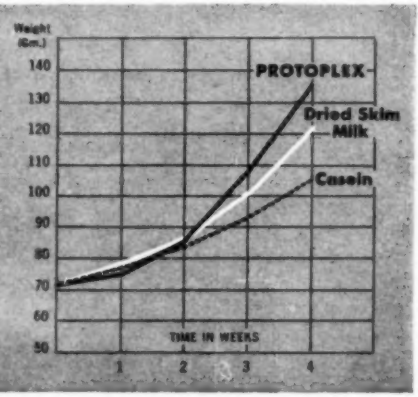
Wyeth®

PROTOPLEX

Whole Mixed Protein plus Whole Liver and Yeast

PROVED BIOLOGICALLY SUPERIOR

to casein and dried skim milk, recognized as standards in protein nutrition—demonstrated in growth studies conducted by an independent, accredited laboratory.



PROTOPLEX* provides all the essential and nonessential amino acids as present in casein, lactalbumin, primary dried yeast U.S.P., and desiccated whole liver. Relatively salt- and fat-free.

Delicious — **Eaten like cereal...may also be incorporated in cakes, biscuits, and waffle batters.**

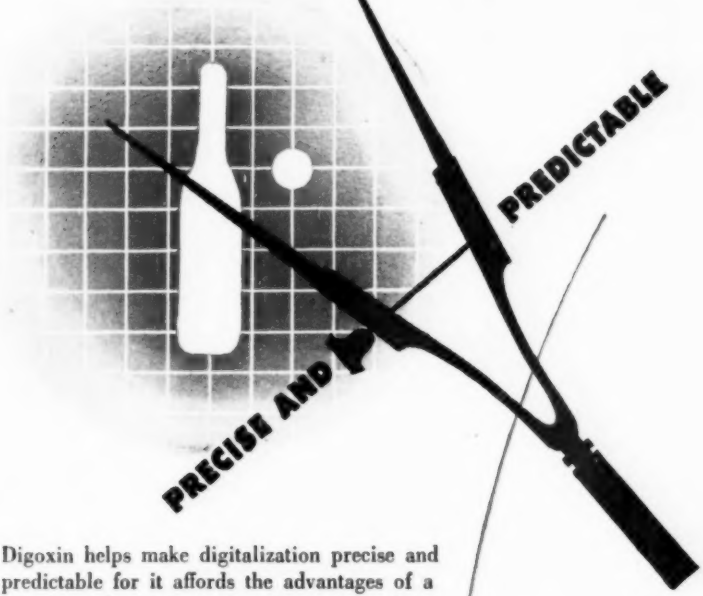
Excellent Tolerance — **An extra 50 to 100 grams of protein daily easily administered.**

SUPPLIED: In 1-lb. packages, available through your local pharmacist.

*Exclusive trademark of Walker Vitamin Products, Inc.

Walker **VITAMIN PRODUCTS, INC., MOUNT VERNON, N. Y.**

digitalization



Digoxin helps make digitalization precise and predictable for it affords the advantages of a pure drug of constant, unchanging potency, thus allowing more accurate administration than is possible with crude digitalis preparations assayed in biological units.

Unvarying in its substance and potency, Digoxin maintains a desirable intermediate position among the rapidly acting glycosides. Rapid uniform absorption provides a means of slow or swift digitalization orally as well as parenterally. Rapid elimination minimizes possible toxic effects.

The average digitalized patient on a maintenance dose of 1½ to 3 grains of whole leaf digitalis per day may be switched to maintenance with Digoxin with an initial trial daily dose of 0.5 mg. (2 'Tabloid' Digoxin) and adjusted subsequently in accord with his needs.

ORAL PREPARATIONS:

'Tabloid' brand Digoxin, 0.25 mgm. (gr. 1/260 approx.) Bottles of 25, 100 and 500.

FOR INTRAVENOUS USE:

'Wellcome'* brand Digoxin Injection, 0.5 mgm. (gr. 1/130 approx.) in 1 cc. Boxes of 12 and 100 ampuls.

**Formerly known as 'Hypoloid'*

DIGOXIN

a crystalline glycoside of digitalis lanata

BURROUGHS WELLCOME & CO. (U.S.A.) INC. 9 & 11 EAST 41ST STREET, NEW YORK 17

A Single Injection Every Other Day

Antibiotic therapy is greatly simplified when C.S.C. Crystalline Procaine Penicillin G in Peanut Oil with aluminum monostearate is prescribed. A single 1 cc. injection (300,000 units) produces therapeutic blood levels for 96 hours in over 90% of patients, *and for 48 hours in all patients*. For certainty of therapy, this preparation need not be given, as a rule, more often than once every other day.

Crystalline Procaine Penicillin G in Peanut Oil-C.S.C. contains 300,000 units of micronized procaine penicillin per cc., together with 2% aluminum monostearate for producing a thixotropic suspension. This outstanding penicillin preparation is free flowing and requires no refrigeration. It is indicated in the treatment of most infectious diseases amenable to penicillin therapy.

Available at all pharmacies in economical 10 cc. size rubber-stoppered vials (300,000 units per cc.), and in 1 cc. size (300,000 units) glass cartridges for use in the C.S.C. Disposable and Permanent Syringes.

96-HOUR
CRYSTALLINE PROCAINE PENICILLIN G
IN PEANUT OIL
WITH 2% ALUMINUM MONOSTEARATE

C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION, 17 EAST 42ND STREET, NEW YORK 17, NEW YORK

criteria in syphilotherapy

"Therefore, more than in any other disease, it is necessary in the treatment of an individual patient with syphilis to follow a therapeutic regimen which, after *long-term study* in *large series of patients*, has been established as *satisfactory* for the particular type of syphilis under consideration."*

MAPHARSEN®

an arsenical of choice in the treatment of syphilis

long-term study

More than a decade of clinical evaluation.

large series of patients

Over two hundred million injections already administered.

satisfactory

High therapeutic effectiveness with notable safety in causing disappearance of spirochetes, healing of lesions and reversal of seropositivity in a large percentage of cases.

MAPHARSEN (oxophenarsine hydrochloride, P. D. & Co.) is supplied in single dose ampoules of 0.04 Gm. and 0.06 Gm., boxes of 10, and in multiple dose ampoules of 0.6 Gm. in boxes of 10.

*Cecil, R. A.: A Textbook of Medicine. Philadelphia, W. B. Saunders Co., 1947, p. 876.

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

MEDICAMENTA VERA · P D & CO.

A *Palatable* Choline . . .

syrup CHOLINE (FLINT)

Representing Choline Dihydrogen Citrate 25% W/V

Your specification "Syrup Choline (Flint)" is your assurance of a stable, palatable product that encourages full patient acceptance and cooperation.

Choline therapy is assuming an increasingly important role in the management of hepatic conditions related to dietary deficiencies, alcoholism, sulfonamide administration, fatty livers associated with toxemias and infections.

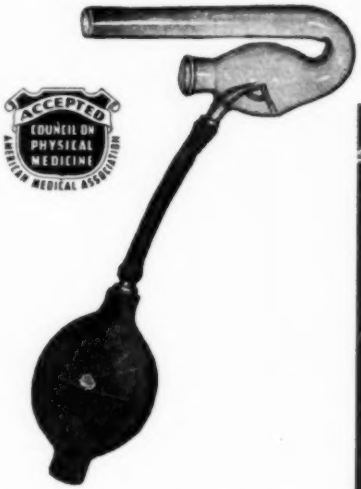
Each teaspoonful of Syrup Choline Dihydrogen Citrate (Flint) presents 1 gram Choline Dihydrogen Citrate. Supplied in pint and gallon bottles.

A COUNCIL-ACCEPTED CHOLINE PRODUCT

For your copy of "The Present Status of Choline Therapy in Liver Dysfunction" write:

FLINT, EATON & COMPANY
DECATUR, ILLINOIS

for inhalation treatment of STATUS ASTHMA



THE I.E.C. NEBULIZER converts bronchodilators in aqueous solution into a mist of microscopic-size particles for inhalation. Immediate and effective penetration of the aerosol to the affected area affords quick relief of the characteristic feeling of constriction and suffocation. The I.E.C. Nebulizer is simple to use involving only the normal respiratory cycle without forced inhalation.

References: A. L. Barach, *M.D., N. Y. State J.Medicine, Vol. 46, No. 9, May 1, 1946.* T. R. Talbot, Jr., *M.D.*, E. H. Quimby, *Sc.D.*, A. L. Barach, *M.D., Amer.J.Medical Sciences, 214, 585–592, December 1947.*

PHYSICIAN'S TRIAL OFFER

At your request we would be pleased to send you the I.E.C. Nebulizer for a 30 day trial. This offer is subject to withdrawal without notice.

WRITE PROFESSIONAL SERVICE DEPARTMENT FOR LITERATURE OR TRIAL OFFER

Inhalational Equipment Company Inc
248 East 119th Street • New York 35, N. Y.

even after 40, a woman's work is never done...

Dishes, dustpans, a thousand details... the three "d's" of household drudgery... are challenge enough at any age, but a stack of dinner dishes can look mountain high to the woman in the menopause. This is a disquieting aspect of the daily life of such patients that physicians can bring into proper perspective with ***"Premarin."***

"Premarin" *therapy, it has been found, has in it a certain "plus" that produces a sense of well-being in most women.* ***"Premarin"*** *quickly relieves the symptoms of the menopause. It is orally active, and is rapidly absorbed from the intestine.*

Ayerst

While sodium estrone sulfate is the principal estrogen in ***"Premarin,"*** *other equine estrogens... estradiol, equilin, equilenin, hippulin ...are probably also present in varying amounts as water soluble conjugates.*

"PREMARIN"

ESTROGENIC SUBSTANCES (WATER SOLUBLE)
also known as CONJUGATED ESTROGENS (equine)

Ayerst, McKenna & Harrison Limited 22 East 40th Street, New York 16, New York
4901

THE AMERICAN COLLEGE OF PHYSICIANS

MEMBERS OF THE BOARD OF GOVERNORS

Term Expiring 1949

Leland P. Hawkins, Los Angeles	CALIFORNIA (Southern)
Ward Darley, Denver	COLORADO
Thomas P. Murdock, Meriden	CONNECTICUT
Wallace M. Yater, Washington	DISTRICT OF COLUMBIA
Cecil M. Jack, Decatur	ILLINOIS (Southern)
Robert M. Moore, Indianapolis	INDIANA
Harold H. Jones, Winfield	KANSAS
Chester S. Keefer, Boston	MASSACHUSETTS
Joseph D. McCarthy, Omaha	NEBRASKA
Edward C. Reifenstein, Sr., Syracuse	NEW YORK (Western)
Wann Langston, Oklahoma City	OKLAHOMA
Edward L. Bortz (*Vice Chairman*), Philadelphia	PENNSYLVANIA (Eastern)
R. R. Snowden, Pittsburgh	PENNSYLVANIA (Western)
John L. Calene, Aberdeen	SOUTH DAKOTA
William C. Chaney, Memphis	TENNESSEE
Louis E. Viko, Salt Lake City	UTAH
Harry L. Arnold, Honolulu	HAWAII
Herbert K. Detweiler, Toronto	ONTARIO
Francisco de P. Miranda, Mexico City	MEXICO
Gilbert M. Stevenson, Ancon	REPUBLIC OF PANAMA and the CANAL ZONE

Term Expiring 1950

Arless A. Blair, Fort Smith	ARKANSAS
Dwight L. Wilbur, San Francisco	CALIFORNIA (Northern)
Benjamin F. Wolverton, Cedar Rapids	IOWA
Edgar Hull, New Orleans	LOUISIANA
Douglas Donald, Detroit	MICHIGAN
Edgar V. Allen, Rochester	MINNESOTA
Ralph A. Kinsella, St. Louis	MISSOURI
Lawrence Parsons, Reno	NEVADA
Harry T. French, Hanover	NEW HAMPSHIRE
George H. Lathrope, Newark	NEW JERSEY
Paul F. Whitaker, Kinston	NORTH CAROLINA
Robert B. Radl, Bismarck	NORTH DAKOTA
Herman A. Lawson, Providence	RHODE ISLAND
Robert Wilson, Jr., Charleston	SOUTH CAROLINA
Ellsworth L. Amidon, Burlington	VERMONT
J. Edwin Wood, Jr., Charlottesville	VIRGINIA
George Anderson, Spokane	WASHINGTON
Delivan A. MacGregor, Wheeling	WEST VIRGINIA
Arthur B. Walter, St. John	MARITIME PROVINCES
Arthur T. Henderson, Montreal	QUEBEC
José J. Centurión, Havana	CUBA

Term Expiring 1951

E. Dice Lineberry, Birmingham	ALABAMA
Leslie R. Kober, Phoenix	ARIZONA
Lemuel C. McGee, Wilmington	DELAWARE
William C. Blake, Tampa	FLORIDA
Carter Smith, Atlanta	GEORGIA
Samuel M. Poindexter, Boise	IDAHO
Walter L. Palmer (*Chairman*), Chicago	ILLINOIS (Northern)
J. Murray Kinsman, Louisville	KENTUCKY
Richard S. Hawkes, Portland	MAINE
Wetherbee Fort, Baltimore	MARYLAND
John G. Archer, Greenville	MISSISSIPPI
Harold W. Gregg, Butte	MONTANA and WYOMING
Robert O. Brown, Santa Fe	NEW MEXICO
Asa L. Lincoln, New York	NEW YORK (Eastern)
Charles A. Doan, Columbus	OHIO
Howard P. Lewis, Portland	OREGON
David W. Carter, Jr., Dallas	TEXAS
Karver L. Puestow, Madison	WISCONSIN
Rafael Rodriguez-Molina, San Juan	PUERTO RICO
John W. Scott, Edmonton	ALBERTA and BRITISH COLUMBIA
Charles H. A. Walton, Winnipeg	MANITOBA and SASKATCHEWAN

Ex Officiis

Raymond W. Bliss	United States Army
Clifford A. Swanson	United States Navy
Leonard A. Scheele	United States Public Health Service
Arden Freer	United States Veterans Administration

℞: only 2 or 3 drops

PRIVINE 0.05%

a distinguished nasal vasoconstrictor

HIGHLY POTENT: Prompt, complete relief from nasal congestion and hypersecretion usually results from only 2 or 3 drops of Privine hydrochloride 0.05%. Each application provides 2 to 6 hours of nasal comfort.

BLAND, NON-IRRITATING: Privine is prepared in an isotonic aqueous solution buffered to a pH of 6.2 to 6.3. Artificial differences in osmotic pressure between solution and epithelium are avoided. Thus, stinging and burning usually are absent.

Privine is generally free of systemic effect. The occasional sedative effect that may be noted in infants and young children is usually due to gross overdosage. Since there is virtually no central nervous stimulation, Privine may be applied before retiring with no resultant interference with restful sleep.

PRIVINE: 0.05% in 1-ounce dropper bottles and 1-pint bottles; 0.1% strength reserved for office procedures, in 1-pint bottles only.

Ciba PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

PRIVINE (brand of naphazoline)—Trade Mark Reg. U. S. Pat. Off. 2/1424M

THE AMERICAN COLLEGE OF PHYSICIANS

1948–49 COMMITTEES

EXECUTIVE COMMITTEE

*Walter W. Palmer, New York, N. Y.
Reginald Fitz, Boston, Mass.
George Morris Piersol, Philadelphia, Pa.
William D. Stroud, Philadelphia, Pa.
Ernest E. Irons, Chicago, Ill.
Hugh J. Morgan, Nashville, Tenn.
Walter L. Palmer, Chicago, Ill.
George F. Strong, Vancouver, B. C., Can.
Charles F. Tenney, New York, N. Y.

ADVISORY COMMITTEE ON POSTGRADUATE COURSES

*Edward L. Bortz, Philadelphia, Pa.
José J. Centurión, Havana, Cuba
Chester S. Keefer, Boston, Mass.
Ralph A. Kinsella, St. Louis, Mo.
Karver L. Puestow, Madison, Wis.

COMMITTEE ON ADVERTISEMENTS AND COMMERCIAL EXHIBITS

*George Morris Piersol, Philadelphia, Pa.
Thomas Klein, Philadelphia, Pa.
Charles C. Wolferth, Philadelphia, Pa.

COMMITTEE ON THE ANNALS OF INTERNAL MEDICINE

*T. Grier Miller, Philadelphia, Pa.
Walter B. Martin, Norfolk, Va.
Cyrus C. Sturgis, Ann Arbor, Mich.

COMMITTEE ON CONSTITUTION AND BY-LAWS

*Ernest E. Irons, Chicago, Ill.
Alex. M. Burgess, Providence, R. I.
Charles F. Moffatt, Montreal, Que., Can.

COMMITTEE ON CREDENTIALS

*George Morris Piersol, Philadelphia, Pa.
A. B. Brower, Dayton, Ohio
LeRoy H. Sloan, Chicago, Ill.
George H. Lathrope, Newark, N. J.
Robert Wilson, Jr., Charleston, S. C.
Wallace M. Yater, Washington, D. C.

COMMITTEE ON EDUCATIONAL POLICY

*William S. Middleton, Madison, Wis.
David P. Barr, New York, N. Y.
Marion A. Blankenhorn, Cincinnati, Ohio

COMMITTEE ON FELLOWSHIPS AND AWARDS

*Reginald Fitz, Boston, Mass.
David P. Barr, New York, N. Y.
Ernest H. Falconer, San Francisco, Calif.
William S. McCann, Rochester, N. Y.
Cyrus C. Sturgis, Ann Arbor, Mich.

COMMITTEE ON ALFRED STENGEL MEMORIAL AWARD

*Maurice C. Pincoffs, Baltimore, Md.
Reginald Fitz, Boston, Mass.
George H. Lathrope, Newark, N. J.
Walter L. Palmer, Chicago, Ill.
Karver L. Puestow, Madison, Wis.
Ex Officiis:
Walter W. Palmer, New York, N. Y.
George Morris Piersol, Philadelphia, Pa.

COMMITTEE ON FINANCE

*A. B. Brower, Dayton, Ohio
T. Grier Miller, Philadelphia, Pa.
LeRoy H. Sloan, Chicago, Ill.

COMMITTEE ON MASTERSHIPS

*William S. Middleton, Madison, Wis.
Charles A. Doan, Columbus, Ohio
Walter B. Martin, Norfolk, Va.

COMMITTEE ON NOMINATIONS

*Maurice C. Pincoffs, Baltimore, Md.
A. B. Brower, Dayton, Ohio
Harold H. Jones, Winfield, Kans.
Chester S. Keefer, Boston, Mass.
T. Homer Coffen, Portland, Ore.

COMMITTEE ON PUBLIC RELATIONS

*Ernest E. Irons, Chicago, Ill.
Alex. M. Burgess, Providence, R. I.
George F. Strong, Vancouver, B. C., Can.
Charles F. Tenney, New York, N. Y.
Walter W. Palmer, New York, N. Y., *Ex Officio*

CONFERENCE COMMITTEE ON GRADUATE TRAINING IN MEDICINE

*Reginald Fitz, Boston, Mass.
LeRoy H. Sloan, Chicago, Ill.

CONSULTING COMMITTEE ON ANNUAL SESSIONS

*Walter W. Palmer, New York, N. Y.
Franklin M. Hanger, Jr., New York, N. Y.
Hugh J. Morgan, Nashville, Tenn.
William J. Kerr, San Francisco, Calif.
Ernest H. Falconer, San Francisco, Calif.
David P. Barr, New York, N. Y.
LeRoy H. Sloan, Chicago, Ill.

HOUSE COMMITTEE

*William D. Stroud, Philadelphia, Pa.
Charles L. Brown, Philadelphia, Pa.
T. Grier Miller, Philadelphia, Pa.

JOINT COMMITTEE FOR THE CO-ORDINATION OF MEDICAL ACTIVITIES

*Ernest E. Irons, Chicago, Ill.
Walter L. Palmer, Chicago, Ill.

* Chairman

Please Mention this Journal when writing to Advertisers

LATEST VITAMIN FACTS

From Merck—where many of the vitamin factors were first synthesized.

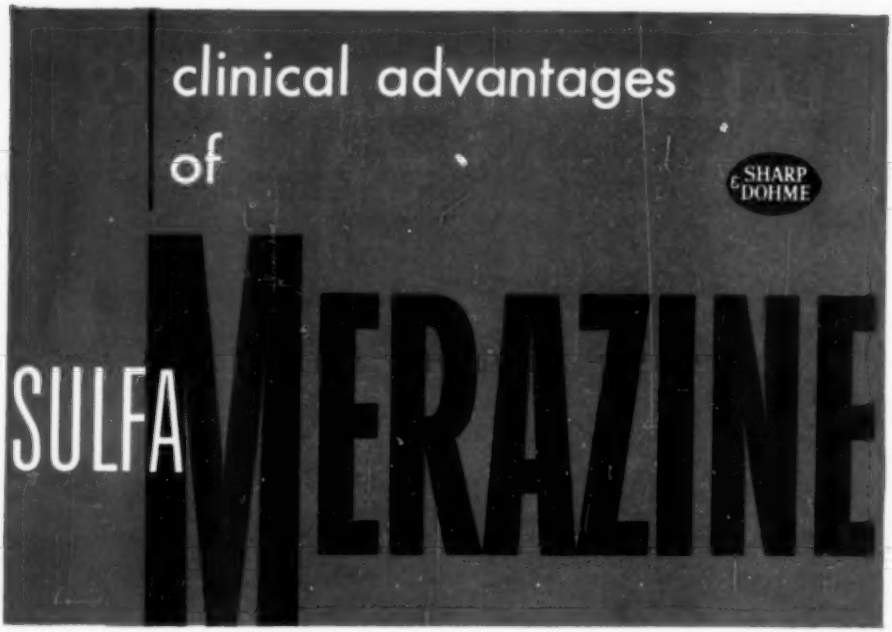
These six Merck *Vitamin Reviews* are yours for the asking while the editions last. These concise reviews contain up-to-date, authoritative facts and can be most useful for quick reference. Please address requests for copies to Merck & Co., Inc., Rahway, N. J.

PARTIAL INDEX OF CONTENTS

- **Factors that produce avitaminosis.**
- **Signs and symptoms of deficiency.**
- **Daily requirements and dosages.**
- **Distribution in foods.**
- **Methods of administration.**
- **Clinical use in specific conditions.**

MERCK VITAMINS

MERCK & CO., Inc. *Manufacturing Chemists* RAHWAY, N. J.



SULFAMERAZINE, a monomethyl salt of sulfapyrimidine developed by Sharp & Dohme research, offers distinct clinical advantages over other systemic sulfonamides in treatment of bacterial infections due to pneumococci, hemolytic streptococci, meningococci, and gonococci:

1/2 Usual Dose

SULFAMERAZINE combats infection with approximately one-half the usual total dosage of sulfadiazine or sulfathiazole.

Fewer Doses

SULFAMERAZINE also maintains effective concentrations in blood and tissues in smaller and less frequent doses than sulfadiazine or sulfathiazole.

Quicker Absorption

SULFAMERAZINE is more rapidly and completely absorbed from the gastrointestinal tract than sulfadiazine or sulfathiazole.

Less Toxic

Experience has shown that SULFAMERAZINE is less toxic than sulfathiazole and slightly less toxic than sulfadiazine.

Supplied in 0.5-Gm. tablets, for oral administration, in bottles of 100, 500, and 1,000; also in ¼-pound packages of powder. SODIUM SULFAMERAZINE, for intravenous administration, is supplied in 5-Gm. vials of sterile powder and in 50-cc. ampuls of a 6% solution. SULFAMERAZINE chemical reagent for laboratory use, is supplied in 1-Gm. vials. Sharp & Dohme, Philadelphia 1, Pa.

SULFAMERAZINE *S. & D.*

ANNALS OF
INTERNAL MEDICINE

VOLUME 30 JANUARY, 1949 NUMBER 1

OUR CHANGING VIEWPOINT ABOUT CONGESTIVE FAILURE *

By ISAAC STARR, *Philadelphia, Pennsylvania*

INTRODUCTION

My old friend "Pete" Abbott, whose untimely death at the height of his powers at the age of 41 was one of the tragedies of American Medicine, used to say that there should be three kinds of scientific papers. In the first the author recounted new facts as he had observed them and drew appropriate conclusions. Papers of this type fill the American medical literature. In the second the author reviewed the literature and this type is also common. But Abbott was conscious of the lack of papers of a third type that he considered equally desirable, a type in which the primary interest is in ideas rather than in facts, and in which the author marshals the evidence which leads him to these beliefs. Papers of this kind are rare in the American literature. Perhaps this is what a most discerning critic, Professor Krogh of Copenhagen, had in mind when he wrote, after visiting this country in 1946; "There is, as I have had occasion to observe, practically no possibility of getting a fairly large, closely reasoned paper published in the United States."

This presentation is emphatically of the third type; I have no new facts to offer for your consideration and I do not intend to review the literature at length. But my ideas about congestive heart failure have been changing. The faith of my fathers, by which I facetiously mean the body of belief about congestive failure taught me in the medical school, has been lost to me, and I can subscribe to it no longer. As doctors must have a system of beliefs if they are to treat their patients logically I am struggling for a new credo, and not altogether satisfied with it. But doctors with patients before them, unlike those engaged in pure science, are constantly being forced to come to an immediate decision, and before we can act thoughtfully and logically, a conception of what is really wrong with the patient is essential.

* Read at the San Francisco meeting of the American College of Physicians, April 21, 1948.

Copyright, 1949, by The American College of Physicians

So, without further ado, I will tell you why I can hold the older conceptions no longer, and of my struggles to reach a new viewpoint. And let me say at once that as my views changed they have become more hopeful. Our failures of therapy in the past may well have been due to misunderstanding of the true nature of the process. Our therapeutic efforts today are much more successful than they were 20 years ago. If we keep our wits about us, and are not afraid of novel ideas and hard thinking, I do not doubt that we will do even better in the near future.

Congestive heart failure is a complex of symptoms and signs which are so familiar that it needs no description to an audience such as this one. The subject could be approached from a number of viewpoints. To those of the descriptive school, heart failure is a group of symptoms and signs; to those of the pathological school, the interest is in the findings at necropsy. But I do not propose to dwell on these viewpoints here, as I myself belong to a new school which is arising and which might well be called the physiological school. I look on heart failure as a physiological process gone wrong and I propose that we consider it from this viewpoint.

Let us concentrate our attention on the cardinal feature which gives the condition its name, the congestion of the greater veins. The veins stand out, swollen with blood and the increased pressure within them can be recognized by palpation alone and measured accurately by any of several methods. The purpose of this lecture is to try to answer several simple questions about this venous congestion, such as: where does the extra blood which over-fills the veins come from, what raises the venous pressure, and especially, what is the relation of this venous congestion to cardiac function? People have been asking these questions for many years so let us start by examining the views held by our predecessors.

One of the oldest and most popular explanations is generally known as the "Dam and Stream Analogy." Described by James Hope in 1842,[1] the Dam and Stream was pictured in Wenckebach's book [2] published in 1937, so the view still underlies the thinking of countless doctors. The blood in the great veins is likened to a pond before a dam in a flowing stream. The heart is thought of as a pump to lift water over the dam. If the heart weakens more water runs into the pond than is pumped out and the pond's level rises.

A second classic experiment was that of Colnheim,[3] who injected oil into the pericardial sac of dogs to handicap the heart, and found that the venous pressure rose.

A third important factor in forming medical opinion was the behavior of the simplest form of a circulation schema,[4] like that illustrated in figure 1. In such a schema if, after pumping hard, one pumps more weakly, the venous pressure rises.

The fourth factor was the behavior of the Starling heart-lung preparation,[5] in which these organs were isolated from the rest of the animal in such

a fashion that the heart would continue to beat for hours, pumping blood past a resistance into a reservoir from which it flowed down to the heart once more. In this preparation as the heart weakens, the pressure in the veins next to the heart, or rather in the tubing which represents them, rises.

The results of these experiments were judged to be concordant and from them was derived a viewpoint so widely held that I always think of it as the classic view. It may be briefly stated thus: A weakening heart is unable to pump the blood from the veins to the arteries in sufficient amount, therefore

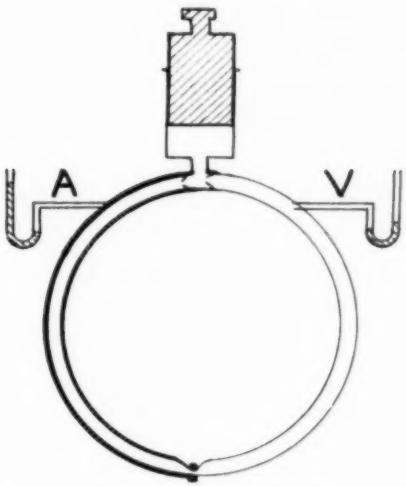


FIG. 1. The simplest form of circulation schema. a. First let us study its behavior as shown. Before the pump is started a pressure of 10 mm. exists throughout the system, this is the static pressure. When one pumps hard the pressures become A = 120, V = 4. When one pumps weakly, the pressures become A = 70, V = 8. Increasing the resistance at the pinchcock increases arterial pressure but always diminishes venous pressure simultaneously, decreasing resistance has the opposite effect. Increased venous pressure together with a maintained arterial pressure cannot be brought about by either weakening the pump, changing the resistance or any combination of the two. b. Let us now inject more water into the system. This lodges chiefly in the most distensible parts, that is, the "veins." The static pressure is now 20 mm. After beginning to pump A = 120, V = 15. Increased venous pressure in the presence of a normal arterial pressure is now attained.

more blood runs into the veins than is pumped out, so the veins become congested and the pressure in them rises. This view has an important corollary: The height of venous pressure is a measure of cardiac strength and weakness, for there was thought to be a direct mechanical relation between the two. Many, probably the majority of doctors, hold this view today. I was taught it with great confidence but I must warn you now that I can hold it no longer.

All this reasoning was done before methods for measuring cardiac output

were available and when these were first applied to the problem discrepancies were soon encountered. The classic view led to the expectation that when the veins were congested the cardiac output would be below normal. And, indeed, on the average this was found to be true.[6] But there were many discrepancies in individual cases; some cases in congestive failure had cardiac outputs estimated to be above normal, and there were many cases of coronary heart disease, hypothyroidism and other conditions which had extremely low cardiac outputs but no venous congestion. Therefore, students of this subject could hold to the classic view only by doubting the accuracy of the estimation of cardiac output, a position that became more and more difficult as these methods were improved; or they could seek for a new theory of congestive failure. Two suggestions can be mentioned at this point; the first view, backed especially by Harrison,[6] sought to explain congestion with a normal circulation by regarding congestive failure as due, not to a diminished cardiac output, but to a disproportion between the strength of the two sides of the heart, peripheral venous congestion being attributed to right heart failure, pulmonary congestion to left heart failure. I cannot support this view myself for reasons which will appear later. The second view was put forward by Altschule[7]; it considered congestive failure to be due to a disproportion between the cardiac output and the metabolic demand for oxygen, and emphasized that congestion with a normal cardiac output occurred when the metabolic rate was elevated. Later work[8, 9] has shown that this is sometimes, but by no means always, true. So, not satisfied by these explanations I was attracted into the field, but before I recount the results of my own studies, let me criticize briefly the evidence which led to the classic viewpoint.

In the Dam and Stream Analogy there is no circulation, a source of power up-stream is assumed. A closer, though still very imperfect analogy is secured by turning the pump up-stream so that its output flows into the pond again, its only source of supply. Under these circumstances one sees at a glance that the rate of pumping would have no effect whatever on the water level of the pond.

In Cohnheim's experiment[3] of cardiac tamponade the venous pressure rose but the arterial pressure fell. This difference from clinical congestive failure did not attract attention because it was universally believed that the arterial pressure fell in clinical congestive failure until about 1905 when the blood pressure was first measured in this condition. But in Landis' somewhat similar experiments,[10] arterial blood pressure was maintained, and I do not doubt this would be a profitable field for further exploration.

In the heart-lung preparation, the venous pressure is dependent on the height of the reservoir. When the heart weakens and stops, its filling pressure must rise to equal the reservoir height. And because the operator keeps the reservoir full, adequate cardiac filling is assured. But there is no assurance of adequate cardiac filling in the intact animal, nor is there any mechanism to support venous pressure as the open reservoir does.

To me, therefore, there was nothing compelling in the evidence which had been offered to support the classic viewpoint. And, as certain clinical observations had made me doubtful of its correctness, I determined to study the subject. As a beginning it seemed wise to study a mechanical model to assure myself that I had a grasp on the purely mechanical factors. Therefore, with the help of Rawson, a model was designed [11] whose pumps behaved in accordance with Starling's law of the heart, and which had both a systemic and a pulmonary circulation. Let me describe its behavior, as simply as I can, and let us ask ourselves what alterations in its behavior will cause it to simulate the pressures found in congestive failure.

First let us consider the *volume changes* of the blood which congests the veins, and ask ourselves where this extra venous blood comes from. The model shows that more than one factor may be at work, and not all the factors are concerned with the heart. We have:

I. Factors dependent on the heart

   a. When the pumps are weakened and the circulation slows, the blood which congests the veins comes *from the arteries.*
   b. When one pump is weakened relative to the other but the circulation maintained, the circuit before the weakened heart gains blood *from the other circulation.* In these two examples the transfer of blood is caused by a change in cardiac function, so I think of them as the *cardiac factors* in the production of venous congestion.

II. Factors independent of cardiac strength or weakness.

   a. If peripheral resistance is diminished by loosening the pinchcock, the veins are congested with blood *from the arterial side.*
   b. If vessels of part of the circulation are compressed from without, blood is driven out of the narrowed parts into the more distensible places, that is into the veins.
   c. If the vessels, other than the veins, should actively constrict, the effect would be the same as b, to drive fluid from the narrowed vessels into the distensible veins.
   d. When extra fluid is injected *from without* it collects chiefly in the most distensible parts, that is in the veins.

Certainly it is easy to demonstrate in a model that the veins may become congested, irrespective of the condition of the heart, which might be beating strongly, weakly or not at all, and so we have *extra-cardiac factors* in the production of congestion. These factors have been summarized in table 1.

TABLE I

Factors in the Production of Peripheral Venous Congestion

I. Cardiac

   a. *Diminished Output*—The excess venous blood comes from the arterial side.
   b. *Weakening Right Side*—The excess venous blood comes from the pulmonary vessels.

II. Non-cardiac

a. *Decreased Peripheral Resistance*—Blood transferred to veins from the arterial side.
b. *Pressure on Vessels from Without*—Blood transferred to the veins from the compressed vessels.
c. *Active Constriction of Vessels*—Blood transferred to veins from the constricted vessels
d. *Increased Blood Volume*—The excess blood accumulates chiefly in the most distensible vessels, i.e. in the veins.

When venous congestion is produced by the last three extra-cardiac factors, it is associated with an increase in the static pressure, a term with which clinicians are usually unfamiliar. The conception behind it I wish to emphasize. The static pressure is the pressure which would exist throughout any circulation when the pump is not working. When one starts the pump of a circulation schema the arterial pressure goes above, the venous below the static pressure. Thus an increase in static pressure raises pressures all around the circulation but this increase is most conspicuous where the pressures are lowest, that is in the veins.

Much of this presentation will be a discussion of the relative weight of these cardiac and extra-cardiac factors in various clinical conditions.

Now let us examine the *pressure* changes when the pump is weakened. In a simple mechanical model (figure 1), when one, after pumping vigorously, pumps more weakly, the pressure in the veins rises, as has long been known. But the pressure in the arteries falls simultaneously and so the pressures that result are not like those of congestive failure as we see it in the clinic, for in these cases the venous pressure is elevated but arterial pressure is maintained. Attempts to reproduce this combination in a schema by weakening the pump, altering the peripheral resistance, or by any combination of both, all fail; any change which puts venous pressure up, puts arterial pressure down and vice versa.

To produce the pressure pattern found in clinical congestive failure one must alter the pressure of the system at rest, the static pressure. This can be readily done by injecting more fluid into the system. Then by starting the pumps we can readily secure the combination sought, a high venous pressure and a normal arterial pressure, as we see so often in the clinic. Raising the static pressure by pressing on the tubing from without accomplishes the same effect.

One is, therefore, unable to reproduce the pressure relations of clinical congestive failure by weakening the "heart," but one does it readily by injecting fluid from without, or by "vasoconstriction." So the results of these experiments point away from the heart and towards other factors in the circulation as the most important cause of venous congestion. These leads were followed up in animal experiments.

Animal Experiments

Although it was well known that the venous pressure of the heart-lung preparation rose as the heart weakened I could find no record that the

crucial experiment had been done in the intact animal, and while my experience with the schema was fresh in my mind, an observation, made during an experiment designed for another purpose, made me resolve to undertake a direct attack. In order to produce abnormalities of form of the ballistocardiograph by directly damaging the heart, I had prepared anesthetized dogs with the chest open, and attacked the right ventricular wall with a cautery until I had almost completely destroyed it; and I was no little surprised to find that only a negligible rise in venous pressure accompanied the maximum damage to the right heart that I knew how to inflict. Therefore the aim of this experiment was changed and it was repeated on other animals by Meade, Jeffers and myself.[12] Also, after losing many animals, we produced as large an infarct in the right heart of a dog as permitted recovery, and followed the venous pressure for 12 weeks without finding any elevation.

The onset of war cut short our experiments but this unexpected result attracted other investigators into the field. In an experiment much similar to ours, Bakos [13] obtained the same results. In a series of experiments, reported as yet only in abstract, Smith and Roos [87] were unable to produce venous congestion in 5 dogs by coronary ligations or widespread coronary embolism with potato starch, but when they first increased blood volume by transfusion, similar cardiac damage resulted in elevated venous pressure and dilatation of the heart with other signs of acute heart failure. Landis et al.[10] damaged the heart by ligature of coronary vessels and by inducing auricular fibrillation without producing a rise of venous pressures higher than controls when the animals were at rest. However, when they were exercised by electrical muscular stimulation the venous pressure of the "cardiac" animals was higher than that of the controls but, unlike patients with congestive failure, as soon as exercise had ceased the venous pressure fell to normal levels once more.

Landis et al.[10] also tried cardiac tamponade and the results came close to what we see in the clinic in cases of constrictive pericarditis. In these experiments the venous pressure rose, as indeed it must if life is to continue, for blood must be forced into the compressed heart against unusual resistance. The relation of these results to clinical congestive failure is not clear to me.

Therefore, it appears that congestion of the veins has not yet been reproduced by direct damage to the heart alone in resting animal preparations although it has by tamponade. Perhaps one should not say it cannot be produced by damaging the heart, but an attempt to produce it by other methods was plainly indicated.

As clinical congestive failure could be simulated in the model by injecting fluid into the circulation, I tried intravenous injections in animal experiments, a field in which many others had preceded me.

In my experiments [14] large intravenous injections of acacia solution elevated venous pressure markedly and if the animal was then killed the "static" pressure was found to be elevated also. So for a time after such

injections the animals had the increased blood volume and the increased venous pressure of congestive failure and after death the increased static pressure also, but they had nothing organically wrong with their hearts.

I cannot, however, claim to have reproduced clinical congestive failure in these experiments because the increase of venous pressure after large intravenous injections was temporary. Perhaps because the injected fluid leaves the vessels, perhaps because the veins slowly dilate to accommodate the extra volume, the venous pressure falls as soon as the injection is stopped, rapidly at first and then more slowly. Landis [10] obtained similar results with whole blood and with Ringer's solution but in one dog he produced a sustained rise of venous pressure after an intravenous injection, a fact which means to me that more work is needed in this field. But I must emphasize the similarity of the condition of animals soon after large intravenous injections to the clinical condition now being called high output failure.

A third method of producing high venous pressure in animal experiments is by asphyxia [15, 12, 10] and, as arterial pressure, cardiac output and venous pressure are all elevated together, we have the right to believe that the effect is due to a widespread vasoconstriction of veins as well as arteries. Whether there is analogy here to anything seen in the clinic is an interesting question.

So we leave the animal experiments with a viewpoint much similar to that obtained from the circulation schema. Increased venous pressure at rest may be caused by contraction of blood vessels, and by increased blood volume, even though the heart is organically sound; and it follows cardiac tamponade as it must if the heart is to be filled at all. But direct damage to the heart muscle of an intact animal does not cause it as long as the animal is at rest, and therefore increased venous pressure at rest is not the direct consequence of cardiac weakness.

Now I am not a person who has great confidence that the results obtained in acute animal experiments can be directly applied to clinical problems so, without too much bias, let us survey the problem from the clinical viewpoint and discuss the experiments and observations made in the clinic.

Clinical Experiments

Some of the experiments I did on animals can be performed in the clinic. The effect of intravenous injection of large amounts of saline and of 5 per cent human albumin solution into volunteers was studied by Warren et al.[16] The results were quite similar to expectations from the animal experiments. Right atrial pressure was elevated immediately after the injection in all instances, to a maximum of 19 cm. H_2O in one case, but the high value was never sustained. Nevertheless, about one hour later this pressure was still considerably above the value found before injection in all subjects given albumin. Again we have evidence that venous pressure can be elevated by increasing blood volume although the heart is normal and the cardiac output at or above the normal level.

The fact that the pressure changes characteristic of congestive failure were produced in a mechanical model only by elevating the "static" pressure, naturally led me to attempt to measure "static" pressure in the clinic.[14] There seemed only one way of doing this: wait until the heart stopped at death and then promptly measure the pressure prevailing throughout the vascular system. This fell off slowly immediately after cessation of cardiac action but a plateau was soon attained and the values secured here in a series of patients are recorded in a previous publication.[14] In those dying in congestive failure the static pressure is elevated sufficiently to account for most, but not all, of the increase of venous pressure found in such cases during life.

These results demonstrate that the larger part of the pressure difference between those with venous congestion and those without it is not due to differences of cardiac action, for with cardiac action out of the picture the differences persist. In our search for the cause of the increased venous pressure in congestive failure, we must look for a factor which persists after the heart has ceased to beat. Again we are led away from thinking of cardiac dysfunction as the immediate cause of the major part of the venous congestion.

The work of two other groups provides an interesting approach to certain aspects of the problem. If venous congestion is due to fluid retention and edema, then edema and gain in weight would precede the increase in venous pressure, but if the increased venous pressure were the first step, then this should occur before edema.

In Stead's clinic,[17] patients who could be kept out of congestive failure by regular injections of mercurial diuretics were followed carefully when the drug was withheld; and edema and weight gain preceded the rise in venous pressure, results which support the view which best fits my own evidence. However, by Reichsman and Grant [18] in Harrison's clinic, a similar type of investigation was carried out on patients dependent on digitalis to keep them out of the congestive state. When this drug was withheld, a rise in venous pressure preceded edema and gain of weight, quite the opposite result from that secured when the mercurials were withdrawn.

Reichsman and Grant [18] suggest that the results of Warren and Stead [17] might be explained by assuming that the latter's patients were dehydrated by the preceding course of mercurial diuretics when the test was begun. But I have frequently observed edema to occur in cardiac patients before any venous congestion was detectable by the usual clinical tests, and many of these patients had had no course of diuretics, so I doubt if this is the explanation. Certainly the field needs further study. Very few patients have been studied so far and when venous pressure is measured simultaneously in both arms of a single subject, the difference in result is sometimes greater than is usually realized. This is a field that any clinician could attack, as no especial apparatus or technic would be required and I hope that data on the important point will be accumulated rapidly.

The results secured after the withdrawal of digitalis [18] are consistent with McMichael's contention that the primary effect of this drug is to cause relaxation of veins. If this view is correct, the results from Harrison's clinic [18] are not inconsistent with the view that the cardiac factor in congestive failure is a small one.

Clinical Facts Concerning Congestive Failure

Before attempting to develop further my ideas on this subject, let us consider together the facts clinicians have gleaned by years of observation of cases of congestive failure, because I judge facts so acquired to be in no wise inferior to those obtained by experiment.

So I propose to state several facts bearing on the problem and then to discuss their meaning. I think these statements are so self-evident that there is no danger of any one of my readers disagreeing with them.

1. *Congestive failure occurs with great frequency in persons with damaged hearts.* This fact is the foundation stone of the view that cardiac damage is the prime cause of congestive failure. It is indeed evidence of the strongest kind but it throws no light on the nature of the relationship. The long interval between the original cardiac damage and the development of congestive failure suggests that the relationship is not an immediate and direct effect.

2. *Digitalis benefits many cases of congestive failure.* To most people the clinical improvement is due to improvement in cardiac function caused by the drug, and that the drug can improve cardiac function in certain conditions of disease seems well established. But we were all taught to give the drug to a case of congestive failure until we obtained a diuresis and certainly great benefit often followed quickly the establishment of this diuresis, so the improvement might be due to fluid loss. McMichael [19] has brought forward evidence that digitalis relaxes the veins, and this action may well afford an explanation for the rapid fall of venous pressure that follows the intravenous injection of the purer preparations.[34, 35]

3. *Examination of the heart at necropsy does not disclose whether the patient died in congestive failure or not.* We have no pathologic evidence which indicates the nature of the relation between congestive failure and heart disease. Thus in Gore's analysis of 143 cases of diphtheritic myocarditis demonstrated at necropsy,[20] congestive failure occurred in only 34 per cent while the majority, 51.4 per cent suffered terminally from a shock-like condition with hypotension, weak thready pulse and imperceptible heart action.

4. *The heart can be severely damaged, as by myocardial infarction, by tumor, or by lesions affecting the muscle and venous congestion does not necessarily follow.* I am sure that instances of this kind are within the experience of every one. I mention it only to emphasize that there is no necessary relationship between venous congestion and manifest cardiac damage.

5. *Most people die without congestive failure.* It seems to me this self-

evident fact has never had the attention it deserved. If diminished cardiac output is the cause of the venous congestion every dying person should show it as the heart's function must diminish before it stops in death. But most persons die without venous congestion so we must conclude either that the cardiac factor is not of sufficient importance to produce manifest congestion of the veins, or that this effect is regularly overcome by another physiological mechanism, such as a general relaxation of vessel tone, which must be assumed to occur as death approaches except when the patient has congestive failure. Regarded in either way it is evident that the cardiac factors are of less importance than the extra-cardiac factors.

6. *Mercurial diuretics greatly benefit patients with congestive failure.* This fact seems to me inconsistent with the classic view. When diuresis followed the exhibition of digitalis or the xanthenes, one could properly argue that the renal action was secondary to a cardiac effect. But the mercurials depress the heart in any concentration known to affect it at all. Lowering of venous pressure, relief of orthopnea and other symptoms promptly follow the action of a drug with no known cardiac effect in the concentration employed. Here again we are led away from the heart in our search for an explanation.

7. *Restriction of Na intake benefits patients with congestive failure.* This fact, together with the benefit occurring from diuretics makes one suspect that the essential thing is to rid the patient of fluid and to prevent its reaccumulation.

8. *In patients in or threatened with failure, pressure over the liver will distend the neck veins.* I mention this fact, it is sometimes used as a test on the continent of Europe, because it demonstrates so clearly that peripheral factors rather than cardiac may exercise the chief control over the height of venous pressure. Certainly the heart's potential strength does not change when one presses over the liver and when the pressure is released, but the venous congestion does. The venous pressure, therefore, is no reliable index of cardiac strength or weakness.

Discussion

It is so much easier to be a destructive than a constructive critic that from my point of view there is much to be said in favor of stopping my presentation at this point. For the old concept that the increased venous pressure was the direct mechanical consequence of cardiac weakness and so a measure of it, seems gone beyond reclaim. But the building of a better conception is another matter. Let us not shirk it, however; indeed we dare not, for patients are dying of congestive failure daily, perhaps due to our ignorance. So let us try to be constructive, not with the idea that our theory will be perfect, but with the expectation that it will be closer to the truth than the conceptions we feel forced to abandon. Let us start by trying out several simple ideas presented as questions.

Does the excess blood in the veins in congestive failure come from the arteries? You will recall that this does happen in the mechanical model when the pump is weakened. Without doubt it takes place in the patient also, but as most people die without congestion of the veins, this factor seems far too small to cause the congestive phenomena we see in congestive failure.

Does the excess blood in the peripheral veins in congestive failure come from the pulmonary circulation? This takes place in the double circulation model when the right heart is weakened but, as an explanation for clinical congestive failure, obviously the answer is no. Pulmonary congestion is found at necropsy, and indicated during life by the reduced vital capacity of cases with congestive failure. But I must point out several facts which bear on what is popularly called right heart and left heart failure.

When you weaken the right heart of a double circulation model, blood is transferred from the pulmonary to the systemic circuits; if the left heart is weakened, the reverse occurs. But in man the pulmonary circulation contains only about one third as much blood as the systemic circuit. Therefore, one has no difficulty in imagining blood from the systemic circuit flooding the lungs, but one wonders whether enough blood could be transferred from the lungs to produce the congestion of liver and peripheral veins that we see in the clinic. Viewed this way, it is of no surprise that maximal destruction of the right heart produced no peripheral venous congestion in my animal experiments. All the evidence indicates that congestive failure cannot be attributed to right heart failure and in my opinion the idea should be abandoned. But the conception that left heart failure is the cause of the pulmonary edema and congestion seen in patients with hypertension appears more soundly based; although I realize that there are difficulties here also.[20]

Are the venous congestion and increased venous pressure of congestive failure due to an increased blood volume and the stretch caused by it? Certainly increased blood volume might explain most of the clinical picture on a purely mechanical basis. The extra blood must go somewhere and it acmulates chiefly in the most distensible vessels, the veins, raising the pressure within them. Capillary pressure is also raised causing transudation of fluid and edema. Edema and excess blood congest and enlarge the liver and other organs. Air space in the lungs is diminished by congestion and edema, gas transport is impeded and this explains the dyspnea which is so characteristic. The excess filling pressure dilates the heart. This conception also explains the persistence of the elevated pressure after death and it is consistent with the results of measurement of blood volume in congestive failure. However, unless the measurements are playing us false, not every case with high blood volume has an elevated venous pressure; in polycythemia vera, congenital heart disease and in some cases of arteriovenous communications there is abnormally large blood volume but the venous pressure is often normal. Therefore, while I believe that the increased blood volume is a factor in the production of the clinical picture, acting alone

it is apparently not sufficient. And were plethora the sole cause, bleeding should cure congestive failure. That it helps some cases is evident, but it is certainly not curative. There must be other factors in the situation.

Is fluid retention the cause of the picture? Excess fluid within the elastic envelope of the skin would press on adjacent blood vessels from without, squeezing the blood into the more distensible parts of the vascular system, and increasing the pressure and congestion of the veins. It is entirely possible that the picture could be explained this way. The most weighty argument in favor of this view is the striking clinical improvement that occurs in so many of these patients when fluid and its contained salts are removed by diuresis, tapping the chest or abdomen, or Southey's tubes. The fall in venous pressure after removal of fluid is often striking. And this conception also provides explanation for the persistence of the pressure elevation after death.

The chief objection to this line of thought will occur to most of you immediately. In many patients with nephrosis we have great retention of fluid but no congestive failure. I suspect this difference to be due to a small blood volume in cases with nephrosis,[36] an adaptation to the great loss of serum albumin into the urine, so that the blood pressed out of the small vessels by pressure from without does not over-fill the great veins.

I would like to digress here to consider another objection that might occur to some. I was taught with great confidence that edema of renal origin was readily distinguished from that of cardiac origin; the first involved the eyelids and face; the latter spared these parts to be concentrated in the dependent parts of the body. It is my opinion that this distinction is not valid evidence of the genesis of edema, and that the difference can be more readily explained in another way. All edema is subject to gravity and the fluid tends to collect where tissue tension is low. Edematous cardiac patients are usually orthopneic and keeping the head up prevents edema from accumulating around the eyes. The nephrotic patient lies flat and fluid accumulates there. I have seen occasional cardiac patients who had edema but not orthopnea; these developed edema of the face when they lay flat. I have also taken a patient with nephrotic edema and made him sleep with the head elevated, and the edema soon left the face and its distribution then resembled that taught as characteristic of heart disease. So I do not believe that a real difference between the clinical characteristics of edema of renal and of cardiac origin has been demonstrated.

Is venous constriction a factor in the congestion? I do not know how to answer this question and I have often thought that a young man might profitably spend his life studying the veins in clinical conditions. We lack a simple clinical method. Arterial pressure is a good indication of arteriolar tone because when the arterioles contract the heart responds to the situation by increasing its work so cardiac output tends to be maintained and arterial pressure to rise. But on the venous side the situation is different: if venous

pressure rises, the cardiac output tends to increase according to Starling's law. Hence if the veins contract the heart may act to keep the pressure from rising and so venous pressure alone is a poor indicator of venous tone. But knowledge of venous pressure and cardiac output would permit an estimation of venous tone, and our knowledge of this subject is just beginning. Employing this method, McMichael [19] concluded that diminution of venous tone accounted for the fall of venous pressure seen in cases of congestive failure when pure digitalis preparations were given intravenously but he made this test on relatively few cases, and his contention that digitalis has no direct cardiac effect is contrary to expectations from pharmacological experiments on the isolated heart. But if one assumes that differences of venous tone do occur in patients, we have a simple explanation for some of the discrepancies we see. Thus, diminished venous tone is an obvious explanation for the failure of some cases with increased blood volume to exhibit high venous pressure, and increased venous tone is a reasonable explanation for that fraction of the elevated venous pressure of congestive failure not accounted for by the elevation of static pressure measured after death.

Are changes in peripheral resistance a factor? Loosening the pinchcock causes the veins to gain fluid in the model, but the arterial pressure falls. Certainly this mechanism is not a factor in most cases of congestive failure as the arterial blood pressure is characteristically maintained. The great majority of such cases have cardiac outputs either normal or below, and arterial blood pressures either normal or elevated. We cannot think of peripheral vasodilatation in these, indeed, the evidence strongly points to peripheral constriction in most of them. Let us remember that peripheral resistance might be elevated in two ways: by a pinchcock-like effect, which would greatly increase resistance but diminish lumen very little and so displace little blood; and by a widespread narrowing of vessels which would increase resistance and displace blood at the same time. The latter may well be a factor in the venous congestion of congestive failure.

We can therefore identify several factors which may play a part in the production of venous congestion but the evidence suggests that each one of them acting alone may be insufficient to cause congestive failure. Perhaps this was to be expected. In the normal subject the veins are in part collapsed and a considerable quantity of blood may be added with little, if any, increase in the pressure within them. We learn this daily when giving transfusions. But once the veins are full, the addition of small amounts of blood would be expected to result in much larger increments of pressure, and in congestion manifest to clinicians. So it is not surprising that single factors, acting alone, are often insufficient to produce manifest congestion of the veins.

I suggest, therefore, that the venous congestion of congestive failure, as we usually see it in the clinic is due to the effect of more than one of the factors mentioned, and that the combination of factors which produces it may vary from case to case.

In the ordinary case of congestive failure one is compelled to believe that increased blood volume and edema are factors because they are so regularly found; that cardiac factors are present because of collateral evidence of cardiac disease. Changes in venous tone are the handiest explanation for such phenomena as the increased venous pressure of cardiac tamponade, during asphyxia and in the agonal rise in venous pressure sometimes seen in the clinic. So the evidence indicates that while the cardiac factor is too small to produce noteworthy venous congestion by itself in resting subjects, acting in conjunction with these other factors it may play a larger part. And even though of small importance during rest, in exercise the cardiac factor increases in effectiveness [10] because, due to the pumping action of the working muscles, more blood may indeed be pumped into the veins than is pumped out by the weakened heart.

However, to some, such reasoning may seem to be beside the point. Although there may be a reasonable way to account for venous congestion with little, if any, mention of the heart, yet one of the most obvious facts about the situation is that congestive failure occurs chiefly in patients long

TABLE II

A Suggested Train of Events Leading to Congestive Failure

1. Heart Disease
2. Diminished Circulation to
   a. Kidney b. Bone Marrow c. Other
3. Retention of Water and Salt
4. Increased Blood Volume
5. Venous Congestion
6. Stimulation of Heart from Increased Filling Pressure
7. Further Damage to Heart

known to have had cardiac abnormality and this is evidence of the strongest kind that heart disease causes congestive failure. I have no intention of denying this and the two conceptions are not inconsistent, if one remembers that causes may be of two kinds, immediate and remote. The facts may be reconciled by thinking in terms of a train of events; I have represented such a train in table 2 and let us now consider it.

I have placed cardiac dysfunction at the top because it so often antedates the congestion. The idea that the train went through the kidney [12] was, of course, suggested by the signs of renal dysfunction, albuminuria, casts, reduced dye elimination, blood urea and nitrogen retention that are so regularly found in congestive failure, and it seemed a short step to conceive that such a damaged organ would not normally eliminate water and electrolytes. And now strong evidence has been secured from Stead's [23] and from Leiter's [24] clinics, using the clearance technics developed by Homer Smith, that the renal circulation is indeed reduced in congestive failure much more than reduction of cardiac output would account for; and there is additional evidence that the elimination of sodium is also much disturbed in such cases.[22, 23]

The idea that the train goes through the bone marrow was suggested by McMichael [25] in 1938 and this view has the advantage of affording a ready explanation for the increased blood volume of congestive failure, because increased blood volume follows exposure of healthy persons to the anoxemia of high altitude.

I mention the possibility of the train going through the endocrine system for two reasons: overdosage of certain adrenal products is well known to cause salt and fluid retention and, in some early experiments apparently not well substantiated, such overdosage was thought to cause a condition akin to congestive failure. And the possibility that the pituitary anti-diuretic hormone plays a part should not be forgotten.

These three routes are not mutually exclusive and from there on the train follows logically enough, but perhaps you will be surprised to note that I have reintroduced cardiac damage at the bottom.

When I was teaching in the course in Pharmacology, we had a student experiment in which, after exposure of the heart for attachment of a myocardiograph, shock was produced by bleeding, and then treated by the intravenous injection of saline and colloidal solutions. Occasionally in an excess of therapeutic enthusiasm, the students would inject saline solution too fast and under too great pressure, with the result that after temporary improvement in its function, the heart dilated and beat feebly; and as instructor in charge, I was forced to intervene to save the experiment by reducing or stopping the intravenous injection, after which the heart soon regained its normal size and beat strongly once more. I have no doubt that everybody who has worked on the isolated or exposed heart of animal preparations has seen it dilate when filling pressure was excessive and Starling made such observations the basis of his Law. To me this experience raises the question whether the increased venous pressure seen so often in the clinic may be a factor in damaging the heart's function by over-distending it.

I do not feel confident that I know the answer to this question and have been searching for relevant facts. Certainly in the clinic we frequently see the heart diminish in size when venous congestion disappears. Doctors have been interpreting this according to the classic view; that is, the venous congestion diminished because the heart's function improved. To me, the alternative view is also possible: the heart diminished in size, and doubtless increased in strength because the venous pressure diminished, just as I have seen the hearts of animal preparations do so often.

I have another reason for introducing heart failure at the bottom of the proposed train of events. When analyzing the relation between congestive failure and the heart, two pitfalls must be avoided. The first when stated baldly sounds naive: The heart must have been affected because the patient died. This viewpoint cannot be laughed off because it points up a distinction which must be drawn before the problem can be visualized clearly. The heart stops beating and the patient is pronounced dead. Obviously, the

heart failed to perform its function of pumping the blood and this failure, absolute in the end, was doubtless preceded by an interval in which it was partial; i.e. the heart beat weakly for a time before it ceased to beat at all. Certainly the heart did fail, but a failure of this type is characteristic of every organ in the body at death. The liver fails at death, but this is not obvious and we are not tempted to diagnose liver disease because of it. But the heart's terminal failure is conspicuous and we are tempted to attribute death to it. In the absence of a clear cause of death clinicians succumb easily to this temptation.

The point is that we must distinguish between primary and secondary effects, if a primary cause is amenable to treatment, the secondary effects take care of themselves. If the secondary effects are corrected, the primary cause remains and the salutary effect is likely to be temporary. This is a most important distinction because on it should be based our efforts at therapy. This paper is a discussion of primary causes of congestive failure with the thought that if it was well understood, treatment would be more effective. Let us not be distracted from our search by the thought that the heart always fails terminally.

The second pitfall is in the old and well known fallacy of the circular argument. Too many doctors, accustomed by training to attribute venous congestion to a weak heart when asked for their evidence that the heart was truly weak are likely to cite the venous congestion. Certainly the evidence already presented convinces me, and I hope you also, that the two are not necessarily associated. You can certainly have a weak heart without venous congestion and, in animal experiments at least, you can have venous congestion without a weak heart. Does the latter occur in the clinic? That is the question before the house.

But if we refuse to accept venous congestion as evidence of cardiac weakness, how are we to identify a weak heart during life, and the answer to this problem is not as easy as some suppose. A history of dyspnea on exertion is relied upon by many but it can also be caused by pulmonary disease or anemia. I think modern clinicians would agree that such evidence as the presence of murmurs, the loudness of the heart sounds, the blood pressure and the palpation of the pulse are of little help; too many irrelevant factors enter into the situation. Fortunately more reliance can be put on other methods.

The electrocardiogram is, of course, the final arbiter in the detection of arrhythmias, and of the greatest usefulness in the detection of local lesions. I have seen no evidence that the minor abnormalities, notching, slurring and T-wave changes have the value which some doctors attribute to them, and certainly no one claims that the electrocardiogram will detect the strength or weakness of the heart.

If you can measure cardiac output you can calculate the heart's work, at least approximately. Here then is a real test of cardiac strength or weak-

ness. These are the methods which hold promise of providing decisive evidence in the future. But we are still in the era of tests made at rest. A diseased heart might be able to perform its work normally while the body rested but be unable to respond properly when more work was demanded of it. While estimations of cardiac output in patients at rest are now becoming commonplace, very few have been reported during or after exercise.

The roentgen-ray is the final arbiter of the size of the cardiac silhouette and if we knew the heart's work as well, we would be in a position to apply Starling's law of the heart as a clinical test of cardiac function.[26] I attempted this as long ago as 1933. Most interesting results were obtained but the methods available at that time were too time-consuming and elaborate for routine use and, although simpler methods are now available, pressures first from the war and later from other duties have prevented me from returning to this field.

Abnormal enlargement of the roentgen-ray silhouette is, of course, important evidence of cardiac dysfunction although one cannot make the distinction between hypertrophy and dilatation and so between strength and weakness. The surprising, and to me unexpected, return to normal of some very large hearts in cases of hypertension relieved by sympathectomy indicates that great enlargement does not necessarily indicate that recovery is impossible.

The course and outcome of the case often appeals to clinicians as being the final arbiter. Certainly in judging the cardiac condition of any case, the development of abnormalities such as arrhythmias and tachycardias, increasing enlargement of the heart and especially repeated relapse after restoration by treatment, should have the attention they rightly deserve. But how tenuous is the relation of such things to cardiac weakness? I think at once of a patient with a history of rheumatic fever who has had very frequent attacks of auricular fibrillation for the last 15 years. Today at the age of 80, to attend the weekly orchestra concert in her balcony seat, she walks up four flights of stairs without a pause and with less dyspnea than is shown by the author walking beside her.

The conclusion of all this might well be that we will have to wait for conclusive evidence on cardiac strength or weakness. But the temptation to postpone decisions must be thrust aside by doctors. The patient waits in the anteroom. In order to be of maximal assistance and to act logically, we must first arrive at a conception of what has gone wrong with him. Let us proceed as well as we can.

Let us attack the problem by boldly accepting the thesis that congestive failure is caused by a train of events outlined and ask ourselves whether this train may be started at other places than its beginning. Can you have congestive failure when the heart is not weak although we concede it might become so late in the course? Let us again ask ourselves a series of questions.

Can the train be started by a renal lesion? Let us consider essential hypertension, in which there is a lesion of the arterioles which might, when far enough advanced, diminish renal blood flow and so start the train leading to congestive failure; and in these cases congestive failure is indeed a frequent event. In some of these cases, I do not know what proportion, the cardiac output is within normal limits during the congestion, so there is no evidence that the heart is weak. And often at necropsy nothing wrong is found with the heart except hypertrophy, and how many ingenious explanations have been brought forward to explain how a heart that gave every indication of being stronger than normal, like the hypertrophied muscles of the blacksmith, was in reality weak. Perhaps the explanation is more simple, perhaps these hearts are really as strong as they appear, perhaps it was the renal lesions, which by diminishing the blood supply to the kidney, started off the train of events leading to congestive failure.

But this explanation does not altogether satisfy me. It is logical to believe that hypertension of itself may damage the heart by overwork, and I have evidence that, as if to keep the heart's work normal in the presence of a hypertension, the cardiac output is often reduced,[26] and this would start the train off itself. Obviously, we are dealing with a complex situation, and congestive failure might be produced by more than one way in cases of hypertension.

Can the train be started by anoxemia per se? I am much interested in the figures given by Richards [9] for cardiac output in cases with congestive failure due to pulmonary disease, and due to rheumatic heart disease. In the first group the cardiac output was normal, in the second it was much reduced. The blood pressures being similar, we can calculate the heart's work roughly and evidently the cases of rheumatic heart disease have weak hearts while those with pulmonary disease do not.

Let me cite a case from my own series.

Case Report

A. G., age 46 in 1948. Between 1940 and 1943 he was exposed to emory dust.

In 1944 he was first admitted with the following findings: Edema of the ankles, cyanosis, dyspnea on exertion. Red blood cells 7.0 to 7.8 mil. Blood pressure 120/85. Roentgen-ray emphysema and cystic changes. Heart normal in size. EKG changes attributed to digitalis. Cardiac output + 17 per cent, after bleeding + 17 and 22 per cent. Rate 70. He was treated by bleeding and radio-active phosphorus and improved rapidly.

In 1945 he was again admitted in congestive failure. The findings were: Red blood cells 5.7. Roentgen-ray, heart moderately enlarged. EKG changes slightly more pronounced. He was treated by bleeding (5750 c.c. in all), digitalis, and mercurials, with rapid improvement.

In 1946 there were three admissions in congestive failure. Most of the findings were as before. Roentgen-ray, heart transverse diameter 19 cm., chest 30.1 cm. EKG no change. He was treated as before. There was rapid improvement each time.

In 1947 he was in failure again. The findings: Red blood cells 7.5 to 8.0, blood pressure 123/68. His pulmonary function was studied by Dr. Julius Comroe. Oxygen

saturation, arterial blood 63 per cent, breathing O_2, 98 per cent. Arterial blood CO_2, 67 mm. Hg (greatly elevated). Respiration 4 liters per min.: normal. Roentgen-ray heart diameter 16.3 cm.; chest 30.1 cm. Cardiac output + 104 per cent. Rate 82. The patient's ballistocardiogram is shown in figure 2. Treated with oxygen inhalations and as before there was rapid improvement.

Apparently pulmonary disease can cause congestive failure without cardiac weakness demonstrable by the tests we now have. So why not consider the anoxemia the prime factor which set the train in motion. However, there is a difficulty which makes me pause. Prolonged residence of normal persons at high altitude causes increased blood volume but congestive failure does not regularly develop, although cardiac cases are well known to

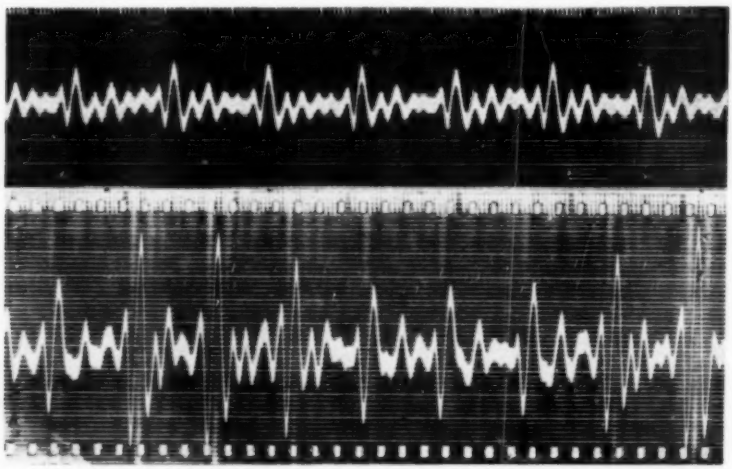


FIG. 2. Ballistocardiograms of a normal subject (*above*—E. P., age 43, 162 lbs.) and of patient A. G. (*below*) described in text. Although he was in congestive failure for the fifth time the patient's impacts are far larger than normal.

do badly at high altitude. Perhaps it is a matter of degree: To obtain anoxemia equivalent to that of my case, one would have to live at an altitude of 22,000 ft. and there are no permanent human habitations above 17,000 ft.

The line of thought suggested by these cases of arterial anoxemia can also be extended to cases of anemia, and perhaps also to cases of hyperthyroidism where the tissue anoxia is not absolute, but relative to the demands for oxygen. In the latter condition congestive failure in the presence of normal or high cardiac output has been reported frequently.

Can the train be started by fluid retention? An observation reported by Brozek, Chapman, and Keys can be considered here. Their group of 34 men, normal in all respects before the event, were subjected to a period of semi-starvation, with a daily intake of less than 1,600 calories. The average

body weight fell 23.9 per cent, the basal metabolic rate to — 39.9 per cent. There was edema during this period, but no venous congestion nor dyspnea on exertion. However, during the recovery period with a diet of 2,500 to 5,800 calories, there was a rise in the average venous pressure which in four men reached 15 cm. of saline or more, and dypnea on exertion became common. One man, released from the experiment after 12 weeks rehabilitation began to eat 7,000 to 10,000 calories per day. Two weeks later he developed edema and dyspnea on exertion and was found to have gained 9 lbs. in the last two days. At this time, the venous pressure was 20 cm. water and the size of the heart had increased sharply. Placed in bed on a diet of 3,000 calories with restricted fluids and ammonium chloride, diuresis soon supervened and he lost 10 lbs. of weight. After this recovery was rapid.

Certainly it is difficult for me to believe that the heart of this subject was weakened by the resumption of food. Is it not much more likely that he simply retained fluid which increased his blood volume, congested his veins and lungs and dilated his heart? After diuresis he was soon normal once more.

The best studied case of beri beri heart disease is that reported by Burwell and Dexter [8] last spring. During the period of venous congestion and acute symptoms, the cardiac output was greatly elevated, over twice the normal resting value, and over twice the value the patient showed after recovering; and when one calculates the heart's work, one finds that this was similarly increased. So here we have congestive failure in the presence of a heart which was not only not weak, but actually beating more strongly than the normal. How was this venous congestion produced? Surely not by cardiac weakness or low cardiac output. Is it not more logical to suppose that it was the retention of fluid which was the primary cause of the high venous pressure and that the effect on the heart was secondary, a stimulation and dilatation such as one sees in the heart-lung preparation when venous filling is excessive?

All of us have been warned that intravenous solutions given too fast or in too large amounts may damage the heart so that the experiment that would prove my point is usually avoided. The best account of it I can find was reported to the Committee on Medical Research in 1945 by Baldwin, Noble, Moore and Richards.[28] In a discussion of the treatment of severe cases of burns by large amounts of saline, plasma and blood intravenously and by mouth they stated "two patients developed an excessively large plasma volume and went into a definitely congestive state with venous pressure of 22 cm. H_2O." Surely it was the increased plasma volume, rather than any cardiac weakness which was the primary cause of the venous congestion.

So I come to the end of my argument. I cannot think of these cases of fluid retention as having weak hearts in the sense that cases of rheumatic heart disease have weak hearts. And there is another striking difference, the cases of rheumatic heart disease after recovery from failure tend to re-

lapse, but the cases of fluid retention, whether from beri beri or over-administration of fluid, once restored to health can be expected to remain healthy. I cannot think of the two types of congestive failure as similar in their fundamentals. And if you will go with me that far, as I think the evidence is becoming compelling, then the whole field is wide open and everyone must ask himself, how much are these non-cardiac factors entering into the case before me? And so I end on a hopeful note, for these extra-cardiac factors are all more readily treated than the muscular weakness to which congestive failure has been directly and solely attributed. Factors directed to the elimination of fluid are becoming more and more successful in handling these cases, and we are only at the beginning of our knowledge of this subject.

BIBLIOGRAPHY

1. Hope, James: A treatise on diseases of the heart, 1842, Lea and Blanchard, Philadelphia.
2. Wenckebach, K. F.: Herz und Kreislaufinsuffizienz, 1934, T. Steinkopff, Dresden.
3. Cohnheim, J.: Lectures on general pathology, 1889, The New Sydenham Soc., London.
4. Starling, E. H.: The Arris and Gale Lectures on some points in the pathology of heart disease, 1897, Lancet, i, 652.
5. Starling, E. H.: The principles of human physiology (revised by C. L. Evans), 1936, Lea and Febiger, Philadelphia.
6. Harrison, T. R.: Failure of the circulation, 1939, The Williams and Wilkins Co., Baltimore.
7. Altschule, M. D.: Pathological physiology of chronic cardiac decompensation, Medicine, 1938, xvii, 75.
8. Burwell, C. S., and Dexter, L.: Beri beri heart disease, Trans. Assoc. Am. Phys., 1947, lx, 59.
9. Richards, D. W., Jr.: Contributions of right heart catheterization to the physiology of congestive heart failure, Am. Jr. Med., 1947, iii, 434.
10. Landis, E. M., Brown, E., Fautex, M., and Wise, C.: Central venous pressure in relation to cardiac "competence," blood volume and exercise, Jr. Clin. Invest., 1946, xxv, 237.
11. Starr, I., and Rawson, A. J.: Role of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. I. Theoretical studies on an improved circulation schema whose pumps obey Starling's law of the heart, Am. Jr. Med. Sci., 1940, cxcix, 27.
12. Starr, I., Jeffers, W. A., and Meade, R. H., Jr.: The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease, Am. Heart Jr., 1943, xxvi, 291.
13. Bakos, A. C. P.: The maintenance of mean pulmonary arterial pressure after extreme right ventricular damage in the dog, Fed. Proc., 1948, vii, 204.
14. Starr, I.: Role of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. II. Clinical and experimental studies, Am. Jr. Med. Sci., 1940, cxcix, 40.
15. Gollwitzer-Meier, K.: Anfallsweise Atemnot der Herzkranken und Hypertoniker, Klin. Wchnschr., 1931, x, 817.
16. Warren, J. V., Brannon, E. S., Weens, H. S., and Stead, E. A., Jr.: Effect of increasing the blood volume and right atrial pressure on the circulation of normal subjects by intravenous infusions, Am. Jr. Med. Sci., 1948, iv, 193.

17. WARREN, J. V., and STEAD, E. A., JR.: Fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure, Arch. Int. Med., 1944, lxxiii, 138.
18. REICHSMAN, F., and GRANT, H.: Some observations on the pathogenesis of edema in cardiac failure, Am. Heart Jr., 1946, xxxii, 438.
19. MCMICHAEL, J.: Circulatory failure, Schweiz. med. Wchnschr., 1946, xxxviii, 851.
20. GORE, I.: Myocardial changes in fatal diphtheria. A summary of observations in 221 cases, Am. Jr. Med. Sci., 1948, ccxv, 257.
21. ERNST, C.: Beitrag zur Frage des Kreislaufes bei der Polycythaemia vera, Ztschr. f. klin. Med., 1930, cxiv, 757.
22. NELSON, W., MAYERSON, H. S., CLARK, J. H., and LYONS, C.: Studies of blood volume in the tetralogy of Fallot and in other types of congenital heart disease, Jr. Clin. Invest., 1947, xxvi, 860.
23. MERRILL, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure; evidence of "forward failure" as the primary cause of edema, Jr. Clin. Invest., 1946, xxv, 389.
24. MOKOTOFF, R., ROSS, G., and LEITER, L.: Renal plasma flow and sodium reabsorption and excretion in congestive heart failure, Jr. Clin. Invest., 1948, xxvii, 1.
25. MCMICHAEL, J.: The significance of cardiac venous congestion, Trans. Med.-Chir. Soc. Edinburgh, 1938, 161.
26. STARR, I., DONAL, J. S., MARGOLIES, A., SHAW, R., COLLINS, L. H., and GAMBLE, C. J.: Studies of the heart and circulation in disease: estimations of basal cardiac output, metabolism, heart size, and blood pressure in 235 subjects, Jr. Clin. Invest., 1934, xiii, 561.
27. BROZEK, J., CHAPMAN, C. B., and KEYS, A.: Drastic food restriction, effect on cardiovascular dynamics in normotensive and hypertensive conditions, Jr. Am. Med. Assoc., 1948, cxxxvii, 1564.
28. BALDWIN, E. DEF., NOBLE, R. P., MOORE, L. V., and RICHARDS, D. W., JR.: Use of fluids in treatment of thermal burns. Analysis of results in 18 cases. Abstract of interim report to the Committee on Medical Research of the Office of Scientific Research and Development. April 3, 1945.
29. LUISADA, A.: The pathogenesis of paroxysmal pulmonary edema, Medicine, 1940, xix, 475.
30. ERICKSON, E. W., and FAHR, G. E.: The effect of lanatoside C upon the physiologic state of organically diseased hearts before symptoms and signs of heart failure appear, Am. Heart Jr., 1945, xxix, 348.
31. STEWART, H. J., CRANE, N. F., DEITRICK, J. E., and THOMPSON, W. P.: Action of digitalis in compensated heart disease, Arch. Int. Med., 1938, lxii, 547.
32. FUTCHER, P. H., and SCHROEDER, H. A.: Studies on congestive heart failure; impaired renal excretion of sodium chloride, Am. Jr. Med. Sci., 1942, cciv, 52.
33. REASER, P. B., and BIRCH, G. E.: Radiosodium tracer in congestive heart failure, Proc. Soc. Exper. Biol. and Med., 1946, lxiii, 543.
34. EICHNA, L. W., TAUBE, H., and DEGRAFF, A. C.: Serial determinations of cardiac output (ballistocardiogram) and electrocardiogram in normal man after intravenous administration of purified cardiac glucosides, Jr. Pharm. and Exper. Therap., 1943, lxxviii, 22.
35. EICHNA, L. W., and TAUBE, H.: The effect of intravenously administered digitoxin and ouabain in the systemic venous pressure of patients with congestive heart failure, Am. Heart Jr., 1944, xxvii, 641.
36. LUETSCHER, J. A., JR.: The effect of a single injection of concentrated human serum albumin on circulating proteins and proteinuria in nephrosis, Jr. Clin. Invest., 1944, xxiii, 365.
37. SMITH, J. R., and ROOS, A.: Production of acute experimental heart failure in dogs with intact circulation, Proc. Am. Soc. Clin. Invest., Jr. Clin. Invest., 1947, xxvi, 1197.

ACHLORHYDRIA AND PEPTIC ULCER: A FURTHER STUDY OF THE RÔLE OF PEPTIC ACTIVITY IN THE PATHOGENESIS AND COURSE OF PEPTIC ULCER*

By William E. Ricketts, Walter Lincoln Palmer, F.A.C.P., Joseph B. Kirsner, F.A.C.P., and Anna Hamann, *Chicago, Illinois*

Introduction

In 1910 Schwartz [1] enunciated the dictum "no acid—no ulcer" the validity of which has been challenged repeatedly throughout the years. The purpose of this paper is to present a further study on the occurrence of ulcer in acid and non-acid stomachs and, more particularly, on the effect of achlorhydria upon the course of peptic ulcer.

Previous studies [2, 3, 4] have tended to establish the invariable presence of acid gastric juice in patients with chronic peptic ulcer and the absence of ulcer in patients with persistent achlorhydria as in pernicious anemia.[5, 6] Washburn and Rozendaal [7] did not find a single ulcer in 906 cases of pernicious anemia nor did Kahn [8] in 840 such cases. Murphy and Howard [9] noted roentgenologic evidence of duodenal ulcer in four of 440 patients with pernicious anemia; apparently the lesion consisted of roentgenologic deformity (scar) rather than an ulcer crater. Rodgers and Jones [10] have described acute transitory erosions and ulcer seen gastroscopically in patients with histamine achlorhydria; these invariably healed or were absent when reexamined a few days later.

Peptic Ulcer and Gastric Secretion

In active duodenal ulcer the question of achlorhydria or even of a low secretory rate almost never arises. Thus in each of 500 consecutive patients with active duodenal ulcer reviewed by us the maximum response to histamine stimulation was above 40 clinical units (table 1). Very occasional instances of duodenal deformity due to scarring have been noted in patients with pernicious anemia or gastric cancer but we have never seen an active duodenal ulcer under such circumstances.

In gastric ulcer the situation is somewhat different. In 170 cases, nine were reported as achlorhydric after the first stimulation with histamine; in all of these, however, free hydrochloric acid was found in subsequent examinations. The lower secretory rates in this group may be seen by contrasting tables 1 and 2. It is noteworthy that in 20 patients the maximum free acidity, even after histamine stimulation, was less than 20 clinical units;

* Presented in part before the Association of American Physicians, Atlantic City, N. J., May, 1948. Received for publication June 26, 1948.

From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

TABLE I

Maximum Free Acidity—Duodenal Ulcer 500
Consecutive Cases—First Histamine Test

	No. Cases	Per Cent
Achlorhydria	0	0
1–20 clinical units	0	0
21–40 clinical units	0	0
41–60 clinical units	16	3
61–80 clinical units	54	11
81–100 clinical units	154	31
More than 100 clinical units	276	55
Total	500	100

in one instance the titratable free acidity was only eight clinical units after repeated stimulation and the lowest pH 3.34, a hydrogen ion concentration adequate for the activation of pepsin. It will be recalled that the gastric pH in complete achlorhydria ranges between seven and eight.[11] Thus these findings are consistent with the concept of "peptic" ulceration. It is clear, however, that gastric ulcer may occur not only without "hyperacidity" and "hypersecretion" but with very low concentrations of acid in terms of response to stimulation with histamine.

TABLE II

Maximum Free Acidity—Gastric Ulcer 170
Consecutive Cases—First Histamine Test

	No. Cases
Achlorhydria	9*
1–20 clinical units	11
21–40 clinical units	16
41–60 clinical units	32
61–80 clinical units	41
81–100 clinical units	32
More than 100	29
Total	170

* Subsequent examination disclosed the presence of free acidity in all 9 cases.

EFFECT OF CONTINUED ACHLORHYDRIA ON THE COURSE OF PEPTIC ULCER

Surgical Achlorhydria. Numerous workers [12, 13, 14, 15] have emphasized the importance of obtaining complete anacidity in partial gastrectomy, for postoperative jejunal ulcer almost never develops after resection for gastric ulcer with its lower secretory acid rate, whereas it does develop after resection for duodenal ulcer and particularly so if complete anacidity has not been attained. We have never seen a jejunal ulcer recurrent after partial gastrectomy without a demonstrable pH of less than 4.0.

Spontaneous Achlorhydria. It has been our good fortune to observe the fortuitous development of complete achlorhydria in two patients with

gastric ulcer, each of whom has been followed for 10 years or longer and subjected to innumerable roentgenologic and gastroscopic studies as well as histamine tests. In neither case did the ulcer recur after achlorhydria became established. In the first patient, the initial ulcer was acute and did not recur; in the second, a large chronic lesion was present and subsequently recurred at intervals until complete achlorhydria appeared; it then healed and has not recurred.

Case 1. Mrs. A. P., a 44 year old woman, was admitted October 10, 1936, because of a burning epigastric distress of four months' duration. A histamine test disclosed a maximum free acidity of 70 clinical units. Roentgen-ray disclosed a small ulceration 4 mm. in diameter in the upper portion of the lesser curvature of the stomach. Gastroscopy failed to visualize the ulcer. The patient was given an antacid ulcer management with relief; the ulcer healed slowly as seen by roentgen-ray, disappearing totally on November 26, 1936. Subsequent histamine tests in the following five years disclosed a decrease in gastric secretion; the ulcer did not recur.

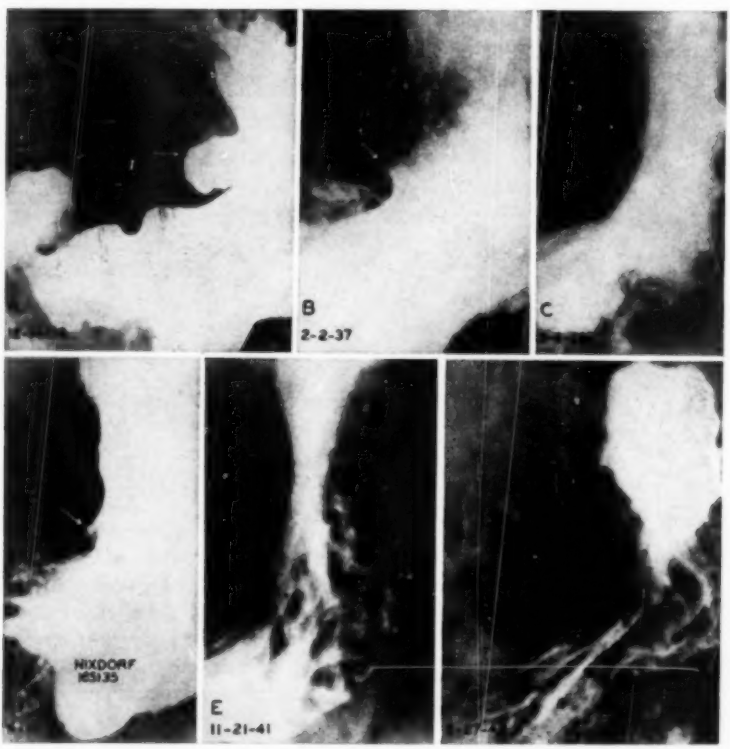


FIG. 1. *Case 2.* Chronic recurrent gastric ulcer, A, B, C, and D. Spontaneous persistent achlorhydria, 1941. No recurrence, E, F.

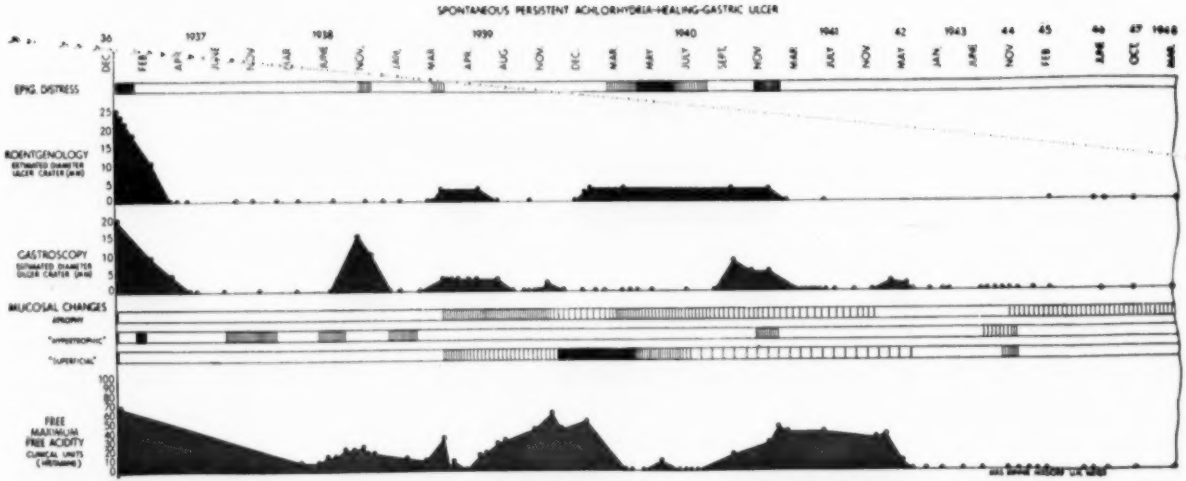


FIG. 2. *Case 2.* Each dot represents one examination; the vertical lines indicate severity of findings, the greater the distance between lines the less the severity; empty block indicates absence of particular findings.

In 1945 when the patient returned because of osteoarthritic pain, histamine achlorhydria was present and has persisted.

Case 2 (Figures 1 and 2). M. N., a 63 year old housewife, first developed ulcer distress in 1934. These symptoms subsided after several weeks of treatment with milk and antacids. Severe ulcer pain recurred in 1936, accompanied by protracted nausea and vomiting. When first admitted in December 1936, the maximum free acidity was 75 clinical units. Roentgen and gastroscopic examinations revealed an enormous penetrating ulcer of the lesser curvature of the stomach. The symptoms disappeared completely during 10 days of antacid therapy. In the subsequent 11 years, 26 roentgen examinations and 55 gastroscopies were performed. The patient's course during the first five years was characterized by recurrent distress and reappearance of the ulcer. However, it is noteworthy and significant that in contrast to the original lesion, the recurrent ulcers were always small and transitory (figure 1); the gastric secretion during these years remained low, never reaching the initial level of 75 clinical units. Since 1941 persistent achlorhydria has been found. It thus appears that as the secretory capacity of the stomach decreased the tendency to ulcer formation decreased. In the seven years since the appearance of complete achlorhydria there has been no distress and no roentgenologic or gastroscopic evidence of ulcer.

Irradiation Achlorhydria. The history of the effect of roentgen irradiation upon gastric secretion need not be reviewed at this time; it has been analyzed elsewhere.[16] Since the observations reported in 1938,[17] we have studied several hundred patients with various purposes in mind, one of them being to note the effect of achlorhydria upon peptic ulcer. The incidence of prolonged achlorhydria following roentgen irradiation is quite low, just how low we are unable to state at present because of the varying technics used and the incompleteness of the data. However, we do have adequate information on 139 patients in whom achlorhydria developed; complete healing of the ulcer occurred in 134 of these. In the 44 patients with achlorhydria lasting longer than 90 days, complete healing occurred in all (table 3).

TABLE III

Healing of Ulcer in Post Irradiation Achlorhydria

	Length of Achlorhydria								
	Less than 30 Days			30 to 90 Days			Longer than 90 Days		
	No. Cases	No. Cases Healed	Per Cent	No. Cases	No. Cases Healed	Per Cent	No. Cases	No. Cases Healed	Per Cent
Gastric ulcer	9	9	100	6	4	66	15	15	100
Duodenal ulcer	40	37	92	33	33	100	29	29	100
Jejunal ulcer	2	2	100	5	5	100	—	—	—
Total	51	48	94	44	42	95	44	44	100

Gastric Ulcer. Of the 30 patients with gastric ulcer in whom prolonged achlorhydria was produced, complete healing occurred in all but two; in these two the achlorhydria lasted only two months and two and one-half

months respectively. Some of the more dramatic and instructive cases of gastric ulcer follow:

Case 3 (Figures 3 and 4). N. B., a 40 year old white painter, first seen in April 1942 for distress of six months' duration, gave a history of recurring attacks of epigastric pain of the ulcer type since 1939. A histamine test (0.01 mg. per kg. body weight) disclosed no free hydrochloric acid. A second histamine test several months later revealed a maximum free acidity of 28 clinical units. A roentgen examination of April 11, 1942, revealed an ulcer situated high on the lesser curvature measuring approximately 22 mm. in diameter and 10 mm. in depth. A gastroscopic examination on April 22, 1942 demonstrated the ulcer. Therapy consisted of ambulatory medical management with milk and cream and powders every hour during the day and atropine 1 mg. at night. With this program the symptoms disappeared for several weeks. The ulcer decreased in size. During the next year the free acidity remained low; occasionally no free acidity was recorded. The ulceration was reported to be healed by roentgen-ray in April 1944. However, it recurred in October of the same year, increased in size and in May 1945 measured 20 mm. in diameter. The patient was admitted to the hospital in May, 1945. Three of four histamine tests failed to yield any free hydrochloric acid; one gave a free acidity of 48 clinical units. Radiation

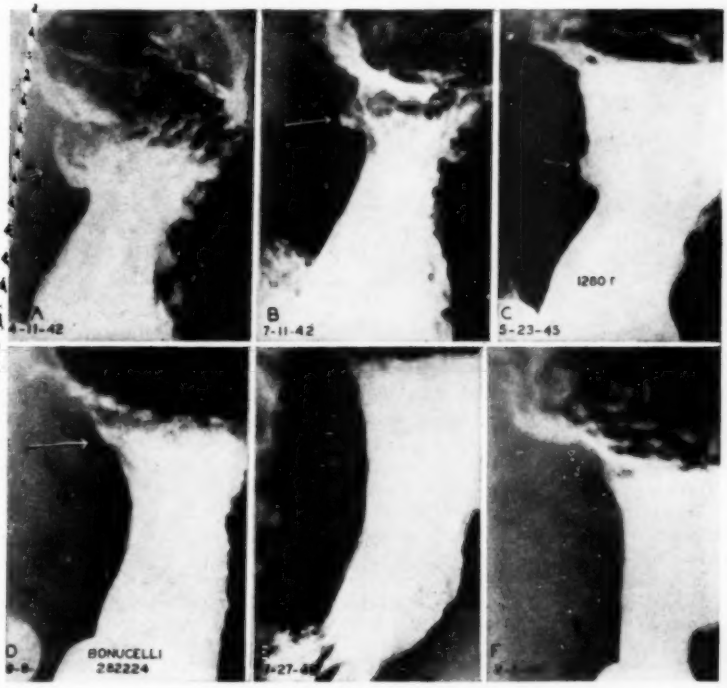


FIG. 3. *Case 3.* Chronic recurrent gastric ulcer, A, B, C, and D. Post irradiation achlorhydria 1945. No recurrence, E, F.

therapy was administered to the fundus of the stomach (total depth dose 1,280 r in 15 days). The response was dramatic; the pain disappeared; the gastroscopic and roentgen examinations revealed a complete disappearance of the ulcer. During the subsequent 32 months the patient has remained well; repeated histamine tests have not elicited hydrochloric acid and the gastric ulcer has not recurred.

Case 4 (Figures 5 and 6). N. O., a 41 year old male iron-worker of Norwegian descent, in 1938 developed epigastric pain from two to four in the afternoon partially relieved by eating. The pain recurred periodically, lasting for several weeks. A diagnosis of gastric ulcer was made in 1941; ulcer management was prescribed with relief from symptoms for six months but the pain recurred. When first seen, in

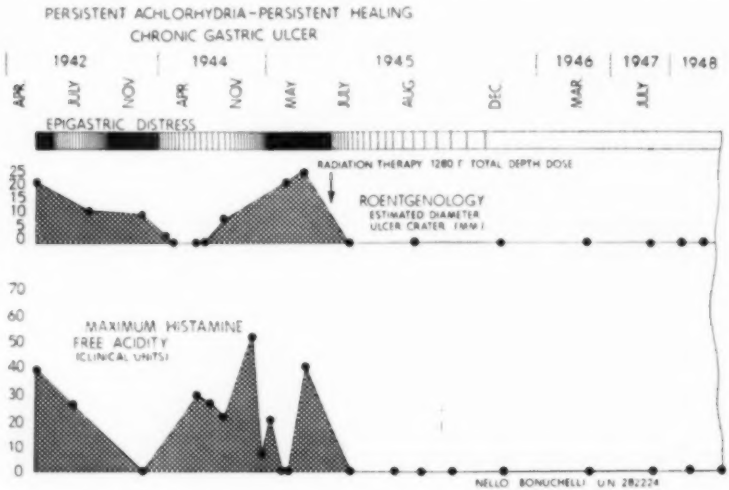


FIG. 4. *Case 3.* Each dot represents one examination.

January 1943, a maximum free acidity (histamine) of 25 clinical units was found. Roentgen-ray disclosed an ulcer 15 mm. in diameter, on the mid portion of the posterior wall of the stomach confirmed by gastroscopy. Ambulatory ulcer management with cream, milk, and powders afford only partial relief. After hospitalization on March 3, 1943 the maximum free acidity (histamine) was 21 clinical units. From March 19 to March 30, 1943 a course of radiation therapy was given with a depth dose of 1,560 r. Progressive decrease in the size of the ulcer was noted by gastroscopy and roentgen-ray; six weeks after completion of the therapy, the ulcer had disappeared completely. On May 19, 1943 no free acidity was obtained after histamine stimulation, nor in repeated tests up to the present time. There has been no recurrence of symptoms or of the ulcer as determined by repeated roentgen-ray and gastroscopic examinations.

Duodenal Ulcer. In 102 patients with duodenal ulcer, complete healing occurred in all but three; in these the achlorhydria lasted less than one month (table 3).

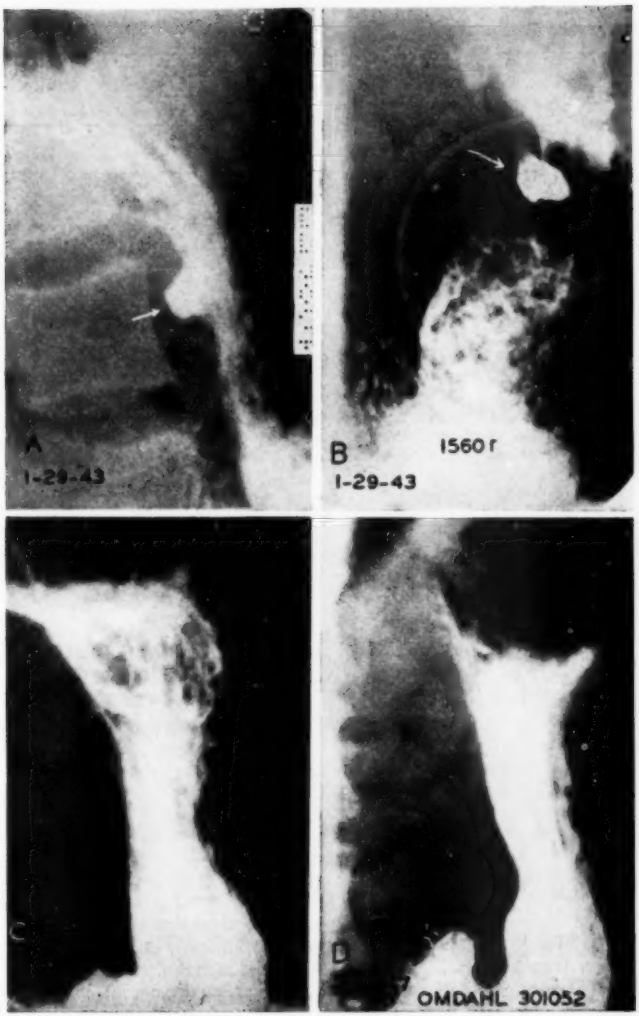


FIG. 5. *Case 4.* Large gastric ulcer, views A and B, healing three weeks after irradiation. No recurrence to date, views C, D.

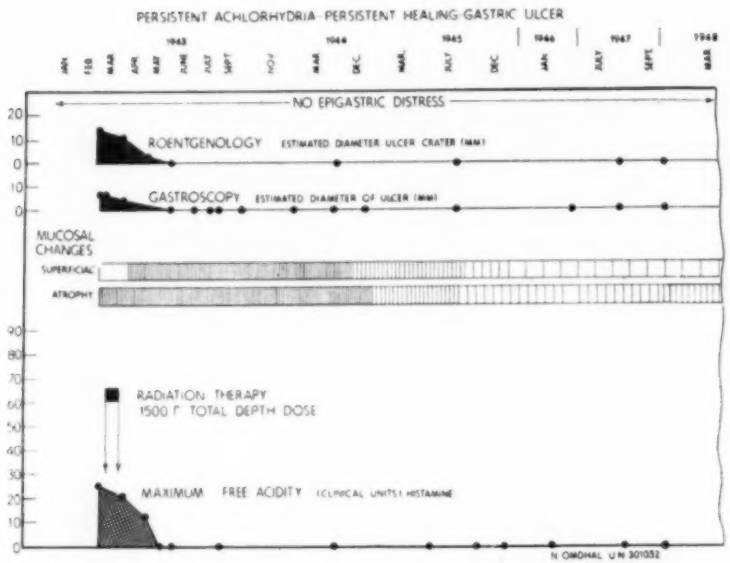


FIG. 6. *Case 4.* Each dot represents one examination; the vertical lines indicate severity of findings, the greater the distance between lines the less the severity; empty block indicates absence of particular findings.

Case 5 (Figures 7 and 8). J. E. C., a 41 year old male clerk, first seen in 1944, had had typical periodic ulcer pain for seven years. In 1937 a roentgen-ray diagnosis of peptic ulcer had been made; ambulatory ulcer management had been given with relief but with numerous recurrences lasting one to several weeks. In 1944 roentgen-ray disclosed an active duodenal and a gastric ulcer, the presence of the gastric ulcer being confirmed by gastroscopy. The histamine free acidity reached a peak of 85 clinical units. Hospitalization and strict ulcer management with hourly administration of cream and milk, calcium carbonate 4 gm. every hour, atropine 1 mg. at night and nightly gastric aspirations gave incomplete relief from the severe continuous pain. Radiation therapy was instituted from December 22, 1944 to January 3, 1945, the depth dose being 1,600 r. The pain disappeared completely. The maximum acidity four days after completion of the therapy was only 35 clinical units; two weeks later no free acidity was found. Roentgen-ray showed complete healing of the gastric ulcer in the second week of February, gastroscopically the ulcer was still present 1 to 2 mm. in diameter on March 14, 1945; it had disappeared completely on April 4, 1945. There has been no recurrence of pain, ulcer or acid in the intervening three years.

Case 6 (Figure 9). J. S., a male office worker, at the age of 35 in 1932 began having periodic epigastric distress lasting for several weeks. In March 1944, he noticed tarry stools. When he was first seen on April 10, 1944, a histamine test disclosed a maximum free acidity of 100 clinical units. A stenosing duodenal deformity with a 4 mm. crater was found by roentgen-ray on April 12, 1944. Radiation therapy, depth dose 1,710 r, was delivered to the fundus and corpus of the stomach from May 4 to May 16, 1944. Achlorhydria developed promptly; the ulcer was reported by roentgen-ray as healed a month after the completion of the radiation. The

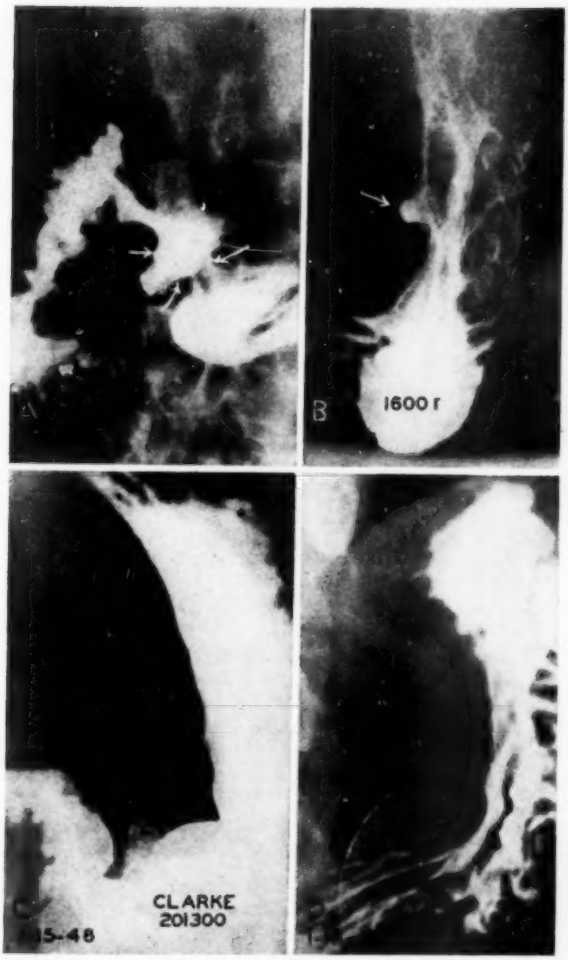


FIG. 7. *Case 5.* Gastric and duodenal ulcers (definite craters seen by roentgen-ray) in January 1945, healing in six weeks after irradiation, no recurrence to date.

patient was entirely relieved of symptoms and has remained so until the present. Since radiation, repeated histamine tests have disclosed achlorhydria each time; roentgen-ray examinations have revealed deformity but no recurrence of the crater.

Delayed Radiation Achlorhydria. In two cases the initial depression of gastric secretion, was not as great as that which occurred later—apparently a delayed reaction due to atrophy of the mucosa resulting from radiation

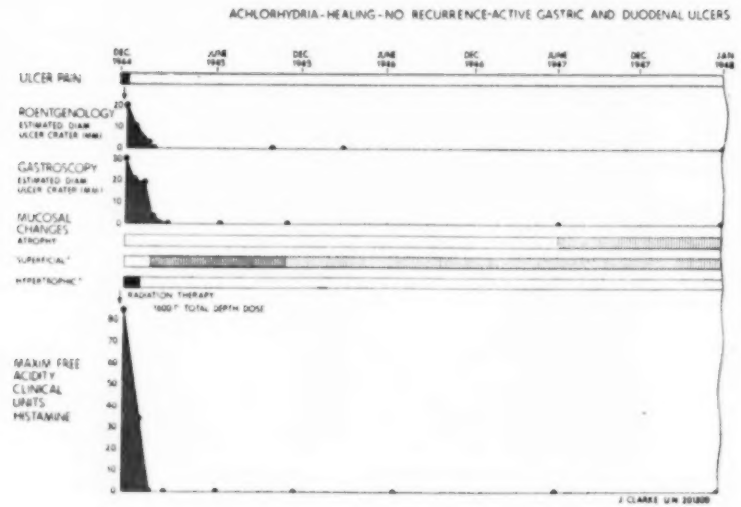


FIG. 8. *Case 5.* Each dot represents one examination; the vertical lines indicate severity of findings, the greater the distance between lines the less the severity; empty block indicates absence of particular findings.

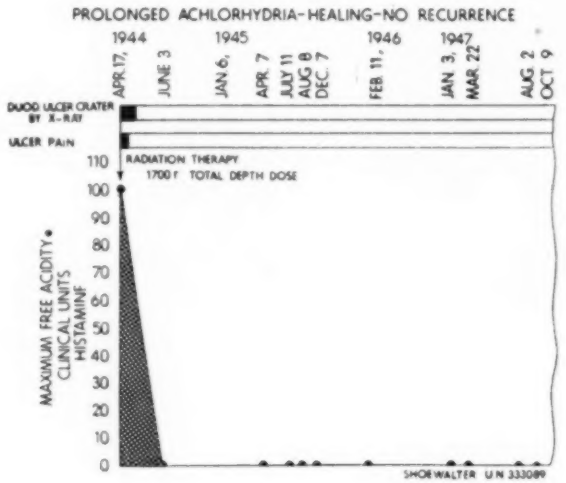


FIG. 9. *Case 6.* Each dot represents one histamine stimulation.

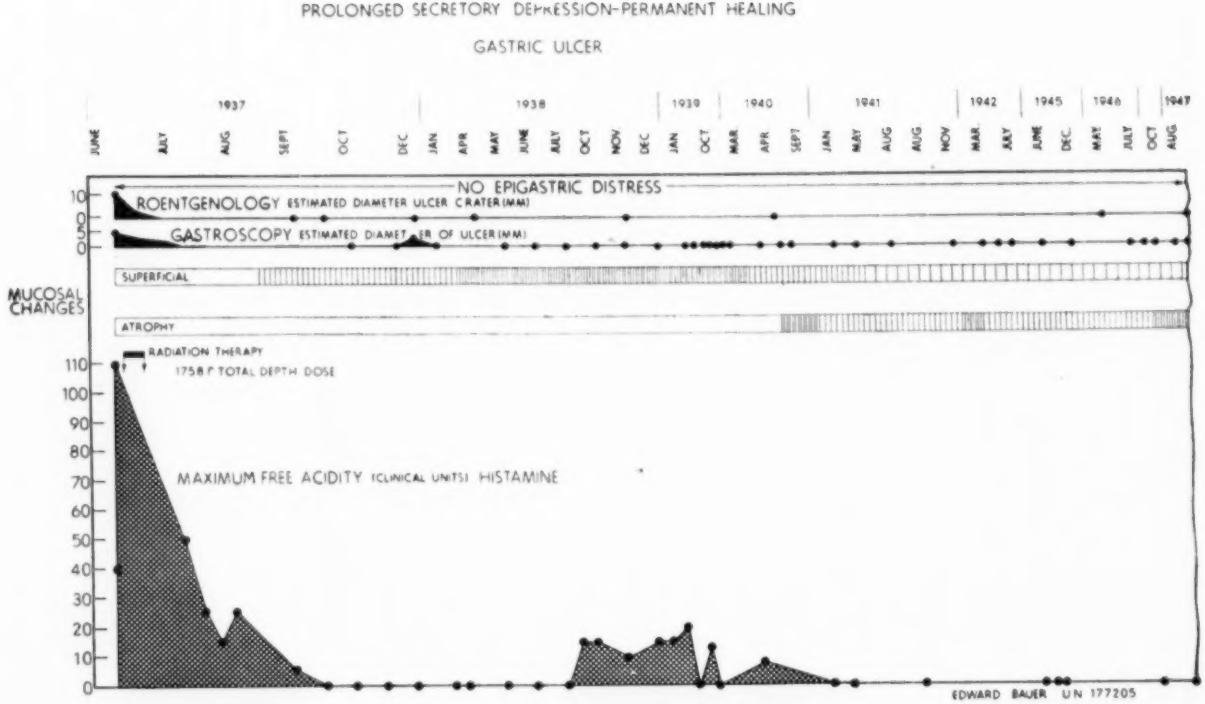


FIG. 10. *Case 7.* Each dot represents one histamine stimulation.

injury.[18] Healing of the ulcer in these two cases was somewhat slower but it occurred in both when complete achlorhydria developed.

Case 7 (Figure 10). E. B., a white male, began having ulcer pain and vomiting in 1930 at the age of 43. The pain lasted from a few days to a week and disappeared entirely after a few months. In January 1937, the pain recurred almost daily, was usually present from two to three hours after meals and was relieved only by the intake of food. He vomited frequently, had a poor appetite, and lost nearly 25 pounds in weight. On admission in June 1937, the gastric acidity after histamine reached a peak of 110 clinical units. On roentgen-ray examination a penetrating ulcer about 1 cm. in diameter was found on the lesser curvature of the stomach near the antrum, confirmed by gastroscopy. On medical management including radiation therapy, approximately 1,758 r, the pain disappeared completely. There was a marked and progressive drop in the acidity until October 8, 1937 when achlorhydria developed. Gastroscopy on October 15, 1937, revealed a disappearance of the ulcer. On December 3, 1937, during the achlorhydria gastroscopy disclosed at the angulus a sharply defined shallow, elliptical, yellowish-gray superficial ulcer; on January 5, 1938 this ulcer had disappeared. No free acidity was recorded at repeated histamine stimulations until September 19, 1938, a peak of 15 clinical units being found. A low free acidity ranging from 0 to 21 units was noted until January 28, 1939, when achlorhydria was again recorded. The patient has had no ulcer distress, no free hydrochloric acid, and no return of the ulcer as judged by numerous roentgenologic and gastroscopic examinations since January 1939.

Case 8 (Figure 11). S. B., a 50 year old white male, began having ulcer pain in 1926 relieved temporarily by a soft diet, but in the following 10 years there were several recurrences. When he was first seen in July 1936 an Ewald test yielded 31 clinical units of free acid. Roentgen examination revealed a large gastric ulcer and a deformity of the duodenal bulb. Gastroscopic examination disclosed a large gastric ulcer. Therapy consisted of a modified Sippy management. The patient improved;

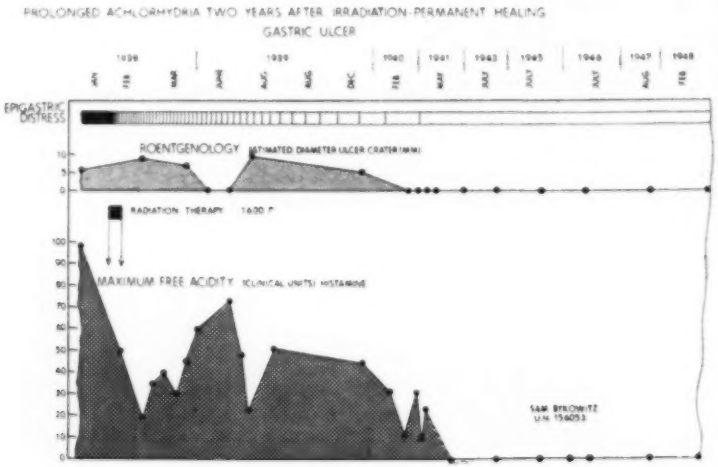


FIG. 11. *Case 8.* Each dot represents one histamine stimulation.

the ulcer diminished in size and in September was no longer demonstrable. During 1937 there were no symptoms, but very small erosions were demonstrated by gastroscopy in May. In October 1937 a definite ulcer was again seen gastroscopically. A histamine test revealed a maximum free acidity of 100 clinical units. A course of radiation therapy directed at the fundus of the stomach was given, 1,600 r depth dose in 13 days from January 12 to January 24, 1938. The free acidity decreased to 20 clinical units and remained low for a short time; two months later 60 clinical units were found. The ulceration healed in June 1939 but recurred in July and persisted for the following one and one half years. In March 1940, although no additional roentgen therapy was administered, achlorhydria was recorded after repeated histamine stimulation. The ulcer visualized by gastroscopy and roentgen-ray until March 1940, healed and the patient was free from distress. From 1940 to the present time the patient has had no recurrence of pain, of acid, or of the ulcer as judged by repeated gastroscopic and roentgenologic examinations.

Jejunal Ulcer. Very few jejunal ulcers were included in the series; the dosage of irradiation was small and prolonged achlorhydria was not obtained.

Recurrent Peptic Ulcer. Recurrent chronic gastric, duodenal or jejunal ulcer has not been observed during persistent achlorhydria whether spontaneous or induced, either by surgery or by roentgen irradiation.

Discussion

The term "peptic ulcer" presupposes the presence of hydrochloric acid for peptic activity occurs only in the acid range of pH, the optimum point being 2.6 [19] with activity decreasing to a pH of five. The "peptic" origin of peptic ulcer has received strong experimental and clinical support in recent years. This paper has dealt with two phases of the problem; the occurrence of chronic ulcer in stomachs possessing a low secretory ability and the effect of complete prolonged achlorhydria on the course of peptic ulcer. Chronic gastric ulcer does occur in patients with transitory achlorhydria and in patients with low secretory ability, but not in complete and permanent achlorhydria. Low acid secretions were noted in 21 per cent of the gastric ulcers studied in this series, but not in a single instance of active duodenal ulcer. Thus peptic ulcer may occur without "hyperacidity" or "hypersecretion" but not with persistent "anacidity."

Further evidence of the validity of the concept of "peptic" ulcer is provided by the invariable healing observed following the appearance of achlorhydria (spontaneous or induced) lasting 90 days or longer, by the very high incidence of healing in phases of achlorhydria of less than 90 days' duration, and by the failure of the ulcer to recur during the period of achlorhydria. It seems evident that if there were a simple means of producing permanent achlorhydria the ulcer problem would be solved. There may be, and doubtless are, other solutions; perhaps a 50 per cent reduction in the gastric secretory rate would be sufficient to produce permanent cures.

The question of why the stomach does not digest itself, asked by John Hunter [20] in 1778, is still unanswered, although much is known about it. The protection afforded the mucosa by the constantly secreted layer of mucus

has been recognized for many years [21, 22] as has the varying susceptibility of the stomach, duodenum and jejunum to peptic digestion. The purpose of this paper has been to focus attention upon the basic problem of "peptic" ulcer by demonstrating the invariable presence of acid gastric content and likewise the invariable healing effect of prolonged achlorhydria.

Conclusions

1. Chronic peptic ulcer occurs only in association with acid gastric secretion.

2. Achlorhydria lasting longer than three months produces complete healing of peptic ulcer irrespective of the age of the patient or the duration of the disease.

3. Spontaneous or induced achlorhydria, if permanent, produces permanent healing of peptic ulcer.

BIBLIOGRAPHY

1. Schwartz, K.: Uber penetrierende Magen- und Jejunalgeschwure, Beitr. klin. Chir., 1910, lxvii, 96.
2. Palmer, W. L.: The mechanism of pain in gastric and duodenal ulcers I, Achlorhydria, 1926, xxxviii, 603–611.
3. Palmer, W. L.: The rôle of acid gastric juice in gastric and duodenal ulceration, Trans. Coll. Phys. Philadelphia, 1942, ix, 191–200.
4. Palmer, W. L., and Nutter, P. B.: Peptic ulcer and achlorhydria. A further study of the role of acid gastric juice in the pathogenesis of peptic ulcer, Arch. Int. Med., 1940, lxv, 499–509.
5. Sturgis, C. C.: Present status of pernicious anemia; experience with 600 cases over 8 years, Ann. Int. Med., 1936, x, 283–289.
6. Goldhamer, S. M.: The gastric juice in patients with pernicious anemia in induced remission, Am. Jr. Med. Sci., 1937, cxciii, 23–28.
7. Washburn, R. N., and Rozendaal, H. M.: Gastric lesions associated with pernicious anemia, Ann. Int. Med., 1938, xi, 2172.
8. Kahn, J. R.: Absence of peptic ulcer in pernicious anemia, Am. Jr. Med. Sci., 1937, cxciv, 463.
9. Murphy, W. P., and Howard, I.: Analysis of complications occurring in series of patients with pernicious anemia, Rev. Gastroenterol., 1936, iii, 98–110.
10. Rodgers, H. W., and Jones, F. A.: Subacute ulceration of stomach associated with atrophy of the gastric mucosa and with absence or diminution in secretion of hydrochloric acid, St. Barth. Hosp. Rep., 1938, lxxi, 140.
11. Kirsner, J. B., Nutter, P. P., and Palmer, W. L.: Studies on anacidity, hydrogen-ion concentration of gastric secretion, gastroscopic appearance of the gastric mucosa, and presence of gastric secretory depressant in patients with anacidity, Jr. Clin. Invest., 1940, xix, 619–625.
12. Wangensteen, O. H., and Lannin, Bernard: Criteria of acceptable operation for ulcer; importance of acid factor, Arch. Surg., 1942, xliv, 489–500.
13. Lewisohn, R.: Gastric resection for duodenal ulcer, Surg., Gynec. and Obst., 1945, lxxx, 355–360.
14. Wangensteen, O. H.: Clinical aspects of ulcer problem with special reference to definition of criteria of suitable operation; importance of short afferent loop, and results of operation, Minnesota Med., 1944, xxvii, 714–722.

15. WINKELSTEIN, ASHER: The significance of the gastric acidity in the surgical treatment of peptic ulcer, Surg. Clin. North Am., 1947, xxvii, 255–260.
16. RICKETTS, W. E., PALMER, W. L., and HAMANN, A.: Radiation therapy in peptic ulcer. To be published.
17. PALMER, W. L., and TEMPLETON, F. E.: Effect of radiation therapy in gastric secretion, Jr. Am. Med. Assoc., 1939, cxii, 1429–1434.
18. RICKETTS, W. E., KIRSNER, J. B., HUMPHREYS, E. M., and PALMER, W. L.: Effects of radiation therapy on the gastric mucosa. To be published.
19. HOLLANDER, FRANKLIN: What is pH? Explanation of various measures of acidity employed in gastroenterology, Gastroenterology, 1945, iv, 497–508.
20. HUNTER, JOHN: On digestion of the stomach after death, Philos. Trans. Roy. Soc., London, 1772, lxii, 447.
21. WHITLOW, J. E.: The protective action of mucus, Master's Thesis Loyola University. (Unpublished.)
22. WOLF, STEWART, and WOLFF, H. G.: Studies on mucus in the human stomach, Gastroenterology, 1948, x, 251–255.

PROBLEMS IN THE NATURAL HISTORY OF POLIOMYELITIS *

By ALBERT B. SABIN, M.D., *Cincinnati, Ohio*

THE people who have worked for many years gathering information on the natural history of poliomyelitis are more impressed with the tremendous amount that remains to be learned than with what is known at the present time. That is not to say that in the approximately 40 years since the discovery of the virus etiology of the disease, there has not been accumulated a great deal of basic information, but what we know is still so sketchy that different investigators can interpret the available data in different ways. In this discussion I shall deal especially with the events which follow human infection with poliomyelitis virus and its mode of spread.

It is no longer mere epidemiologic hypothesis to regard paralytic poliomyelitis as only one part of the clinical spectrum which results from infection with poliomyelitis virus. Although there are as yet no simple tests for poliomyelitis infection in the individual case, the data very laboriously collected thus far suggest that following introduction and multiplication of the virus in the human body the following events may ensue: (1) no obvious signs of disease, (2) a febrile illness of one to seven days' duration associated with any one or all of the following symptoms—headache, mild sore throat, nausea, vomiting, abdominal pain, (3) the preceding syndrome plus distinct nuchal or spinal rigidity, and (4) the preceding syndrome with varying degrees of paralysis and other signs indicative of involvement of the central nervous system.

Let us now examine the extent of our knowledge on the behavior of poliomyelitis virus in the human body which would explain this clinical spectrum and also provide a basis for our evaluation of the various potential modes of spread. Our information for this kind of synthesis must be derived chiefly from studies on human beings—during life as well as post mortem—although it is obvious that the answer to certain questions on pathogenesis can come only from judiciously designed animal experiments. The few observations which were available on human beings only 10 years ago and the injudicious deductions from animal experiments led to a concept of human infection which limited the field of operations for the virus to the olfactory mucosa and certain parts of the central nervous system. This concept was given up, as is well known by now, because both virus assay [1, 2] and pathological studies [3, 4, 5] on fatal spinal and bulbar paralytic cases showed that the

* Morning lecture delivered at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 21, 1948.

From the Children's Hospital Research Foundation and Department of Pediatrics, University of Cincinnati College of Medicine.

Personal work reported in this communication carried out with the aid of The National Foundation for Infantile Paralysis.

pattern in human beings did not correspond to that found in monkeys [6] and chimpanzees [7] infected with poliomyelitis virus by the olfactory pathway. Although analogies are sometimes very helpful for orientation they also have their limitations. Certain phenomena in poliomyelitis, such as the well-established excretion of the virus in the stools, have been compared with pulmonary tuberculosis, scarlet fever, etc. where the etiological agent may be similarly excreted without it constituting a significant factor in the transmission of the disease. We must ask ourselves then whether or not poliomyelitis is in other respects also like pulmonary tuberculosis or scarlet fever or measles? Does the poliomyelitis virus multiply in or reach the lungs, the trachea, the nasal mucosa in any significant amounts?

It should be pointed out here that the death of the "olfactory pathway" concept of poliomyelitis has not eliminated from consideration the respiratory tract as the chief extraneural system involved in poliomyelitis, as reference to the most recent epidemiological literature will make clear.[8, 9, 10, 11] What, then, are the facts with regard to the peripheral sites in which poliomyelitis virus is demonstrable with regularity in human beings—dead or alive? Since much of the controversy or indecision centers around the respiratory tract versus the alimentary tract it may be well to draw the line between them anatomically, particularly where they cross each other in the oropharynx. For this reason one must consider separately results obtained with nasal secretions and nasal mucosa from those with so-called "nasopharyngeal secretions or washings" in which material from the oropharynx is obviously included. Results which are regularly obtained only with material from the oropharynx and *not* with that derived from the nose or lower respiratory tract seem to me to belong more appropriately in considerations of the alimentary tract. Prior to 1941, there were only scattered reports in the literature of tests on this or that tissue from fatal cases of poliomyelitis, and in the earlier days care was not always taken to avoid contamination.[12] A systematic study of the topography of the virus throughout the body of seven patients, who for the most part died within a few days after onset of symptoms, was reported in 1941 [1] and a still more extensive study of the localization of the virus in various levels of the alimentary tract was carried out subsequently on six additional fatal cases.[13] As is well known by now, these studies established the fact that the washed tissues of the alimentary tract were the only sites in which the virus was *regularly* found outside of the central nervous system. When multiple levels were tested the virus could be found somewhere in the tissues of the alimentary tract in each patient. In any given case the virus was detected only in the pharynx or only at some level of the intestinal tract or in both, and this without reference to whether the primary paralysis was bulbar or spinal. It cannot be stressed too often that in no instance in these studies was virus found in the nasal mucosa. In the entire literature on poliomyelitis there is only a single report made by Flexner and Amoss [14] in 1919 in which the virus was said to have been re-

covered from the nasal mucosa of one of three fatal cases tested. In view of Flexner's statement [12] in 1936 that in the earlier years admixture with positive tissues could not be ruled out, and since it is also possible that during the terminal state there may be contamination of the nasal mucosa with material from the oropharynx, it is difficult to assign too much weight to this single finding, particularly since tests in later years on washed tissue removed with special care to avoid contamination yielded only negative results. It is also noteworthy that in no instance was virus recovered from the salivary glands or the urinary bladder of human cases, in whom poliomyelitis virus was readily demonstrated elsewhere in the body. Nor with all the possibilities for aspiration, has the virus been demonstrated unequivocally in the trachea or lungs.[1, 13] The pattern of virus distribution in a series of cases is more important than any isolated positive finding, and the almost regular or constant absence of virus in certain parts of the body cannot be dismissed from consideration on the grounds that negative findings are of no significance, when the same methods and procedures have served to demonstrate the almost regular presence of the virus in other peripheral tissues of the same individuals.

Nevertheless, it is known from studies on the pathogenesis of other neurotropic virus infections in experimental animals, that the pattern of virus distribution may be quite different early after invasion and before involvement of the central nervous system, from that which may be found at death. It is important to examine, therefore, what is known about the presence of poliomyelitis virus in the human body during life and particularly during the earliest stages of the infection. As regards the blood the early reports were all negative, and more recent work [15] with concentrated, ultracentrifuged preparations from 111 patients, most of them bled within a few days after onset of symptoms and 20 within less than 24 hours, yielded a positive result in a single abortive or nonparalytic patient. No virus has been found in the urine.[2, 16] The nasal secretions alone, as distinguished from combined nasal and pharyngeal washings commonly referred to as "nasopharyngeal secretions," have been studied on two occasions in 41 patients and have not yielded a single unequivocal positive result. In one of these studies on 22 paralytic patients [16] the pooled secretions collected on multiple cotton plugs inserted deep in the nasal cavities over a period of three consecutive days, failed to yield virus even when the collections were started within three days after onset of first symptoms. Similar negative results were obtained with the saliva and oral secretions expectorated naturally without hawking or coughing over a period of three days by 20 paralytic patients. However, single specimens of stools or enemas obtained at the termination of each three-day period yielded virus in 10 of these patients.

In the second study [17] on 19 patients, all within four days after onset of symptoms, the throat and nose were swabbed separately after, however, the

patients had been induced to talk, blow, cough and expectorate for one-half hour into sterile gauze masks which were tied over the patient's mouth and nose. The throat swabs yielded virus in six of these patients, the nose swabs in one, and the wet portions of the masks in two. Since the same patient who yielded the positive nose swabs also had virus in the mask and since the nose was swabbed after the mask had been contaminated, the authors [17] are not willing to interpret this result as an unequivocal demonstration that virus is present in the nose under normal conditions. The report of Kessel and his associates [2] that only negative results were obtained in tests on nasal washings from 139 patients is of interest in this connection, especially since it is not clear that they may not have dealt with nasopharyngeal rather than nasal washings. The repeated demonstration of virus in the tissues of the oropharynx and in washings from this region [18, 19, 20, 21] particularly during the early stages after infection, can hardly be used as evidence for involvement of the respiratory tract in poliomyelitis. The oropharynx is properly part of the alimentary tract and the intriguing point in the available observations lies rather in the fact that virus is only infrequently recovered from this region after the first week, while the stools continue to be infective for many weeks.[22] In this respect Dr. Thomas Francis has often recalled in recent years the almost forgotten reports [23, 24] that typhoid bacilli could be recovered from the throat and mouth of approximately 50 per cent of patients with typhoid fever. Since the work of Hamburger and his associates [25] has shown how limited is the escape to the exterior of streptococci and presumably other infectious agents which are present only in the throat, and that the "nasal carriers" are the "dangerous carriers" from the point of view of dissemination, it would appear to be of the greatest importance to establish as unequivocally as possible by further studies on patients in the earliest stages after infection the extent to which the nasal mucosa and the oral secretions under ordinary, not artificial circumstances, may be a source of poliomyelitis virus. If the present negative results are confirmed, it should have a bearing not only on epidemiological thinking but also on public health practice.

For the present, however, our chief concern in the pathogenesis of the infection is with how the virus which is demonstrable in various levels of the alimentary tract gets there and where it multiplies during the many weeks of its excretion in the stools. The simplest assumption would have it that as virus is swallowed it invades the tissues at one or another or many levels of the alimentary tract and multiplies locally. That poliomyelitis virus can pass through the secretions of the stomach and intestines unharmed has been shown many years ago, but when it failed to multiply as with certain strains in rhesus monkeys, it could not be detected in the stools for more than two to three days after feeding.[26] There are, however, certain difficulties connected with the hypothesis of local multiplication. There is at the present time no evidence that the virus can multiply in any cells other than nerve cells, and because of the extreme host and tissue specificities of the polio-

myelitis viruses it would be most difficult to devise an experiment with an appropriate strain of virus that could answer this question unequivocally. Certain it is, however, that the mere capacity for even extensive multiplication in nerve cells is not sufficient to insure multiplication in the alimentary tract. Some of the strains of virus that are most highly virulent for either the rhesus, cynomolgus or African green monkeys, among them the well known M. V. strain and the Brunhilde strain of Howe and Bodian, pass through the alimentary tract of these animals without either local multiplication or production of the disease.[27, 28] Certain other strains of recent human origin, however, such as the "Per," produced the disease quite readily after being fed in the form of cynomolgus nervous tissue to cynomolgus monkeys and could be detected with great ease throughout the entire alimentary tract —washed tissues as well as contents—at the onset of paralysis.[13] Similar results were obtained by Faber [29] with this strain of virus, but after only a few additional passages in rhesus monkeys Howe [30] was unable to infect any of a large number of cynomolgus monkeys with this strain.* The successful infection of chimpanzees by the oral route with human stools [31] as well as with a variety of monkey-adapted [32] and also mouse-adapted poliomyelitis viruses [33] is now well established, as is the fact that chimpanzees like human beings can then excrete the virus in their stools for as long as two months.[32] It is clear, therefore, that a poliomyelitis virus must possess some property in addition to its neurocytotropism as measured by its virulence for the central nervous system, in order to be able to multiply in or invade from the alimentary tract. Thus while the submucous and myenteric plexuses of nerve cells, which are so abundantly distributed in the alimentary tract, might be considered as the sites for virus multiplication, it is not clear why they are not attacked by all virulent strains. Although it is conceivable that virus multiplication could occur without necessarily destroying these nerve cells, it would have to continue over a much longer period than is ordinarily the case in the central nervous system.

Faber and Silverberg [34] recently postulated that "almost any nerve system with peripheral endings in the mucous surfaces *can*, if exposed, convey virus in a central direction to its regional ganglia" and that "the primary lesion of poliomyelitis occurs in the peripheral ganglia." According to this view there is no local multiplication at all at the portal of entry, and the presence of virus in the peripheral tissues would be due to a retrograde centrifugal axonal spread from the first neuronal cell bodies affected by the virus. In my opinion, the greatest difficulty in the way of this attractive hypothesis is the fact that highly virulent strains of poliomyelitis virus cannot invade the central nervous system of rhesus monkeys from either the nasal, pharyngeal or intestinal mucosas when the olfactory tracts are cut, and even more recently

* Since the presentation of this paper, Howe and Bodian (Am. Jr. Hyg., 1948, xlviii, 99–106) reported that while "Per" virus derived from rhesus monkeys failed to infect cynomolgus monkeys by the oral route, that derived from cynomolgus monkeys produced such infection with the same incidence as originally reported by Sabin and Ward.[27]

recovered strains such as Howe and Bodian's "Brunhilde" virus, in spite of possessing an intracerebral titer of $10^{-5.4}$, failed to multiply in or penetrate the mucous surfaces of the alimentary tract after being fed to baby African green monkeys.[28] It cannot be said, therefore, that all that is required is a virulent virus and any mucous surface with exposed nerve endings.

The observations of Trask and Paul,[35] later extended by Melnick,[36] which showed that in occasional chimpanzees and monkeys inoculated with certain strains of virus intracutaneously, subcutaneously or intraperitoneally (but as a rule *not* after intracerebral inoculation) virus may subsequently be recovered from the stools, suggested that virus may localize in the alimentary tract without necessarily being swallowed. That such localization is most likely not due to centrifugal spread from the central nervous system is suggested not only by the fact that virus could be found in the stools several days before the appearance of paralysis,[36] but that following the extensive multiplication of virus which occurs after intracerebral inoculation, the virus has never been found in the stools by other investigators [26, 37] and only once in Melnick's[36] tests on 28 monkeys. Although one wishes that these animals in New Haven had not been exercised "in a common runway" where they might have picked up some virus from the feces of other monkeys (such spontaneous infections have now been reported [38]), it is, nevertheless, possible that in occasional parenterally inoculated animals the virus could enter the blood stream [13, 27, 39] and then localize in the alimentary tract. In young mice inoculated intravenously with the virus of St. Louis encephalitis it has been demonstrated that almost simultaneous localization and multiplication occurred in the intestinal tract and brain.[40] It may be noted parenthetically, however, that despite extensive multiplication in the intestines, the St. Louis virus was not excreted in the stools.

As regards the pathways by which the human nervous system is invaded from the periphery, the available bioassay and pathological studies have led Howe and Bodian and myself to agree that they only serve to exclude the olfactory system and the blood stream as possible pathways of the virus and to suggest that the cervical and abdominal sympathetic nerves are infrequently if ever used as pathways for invasion of the central nervous system.[5] The frequency with which the bulbar form of the disease is exhibited by monkeys inoculated into the pharyngeal region [41] and by patients who develop poliomyelitis after tonsillectomy,[42, 43] and the small proportion of the bulbar type among the general run of cases, perhaps suggests that the nerves of the pharynx do not constitute the most frequent pathway. The same objection may perhaps be raised against the vagus nerve, which supplies almost the whole intestinal tract except for the descending colon and rectum, even though there is experimental evidence that primary spinal paralysis may occur in a proportion of animals, in whom viral invasion occurred along the nerves of the throat [41] or the vagus.[44] Since nuchal and spinal rigidity or spasticity are almost invariably found before the appearance of paralysis,

and since Bodian [45] has recently reported that in the preparalytic stage of experimental poliomyelitis, spasticity, tremor and hyper-reflexia of the leg muscles can occur in the absence of virus or lesions in the lumbar spinal cord, but apparently as a result of lesions in the reticular formation and vestibular nuclei of the medulla and the roof nuclei of the cerebellum, it may be that the medulla is the primary site of invasion in the human central nervous system. On the other hand, the not infrequent history of regional cutaneous hyperesthesia, sometimes for several days prior to the development of primary lower spinal paralysis, has suggested that there may be primary involvement of the dorsal root ganglia via the afferent sensory fibers from the gut; the difficulty with this hypothesis is that there is still some question among anatomists as to whether or not there are sensory fibers in the gut with cell bodies in the dorsal root ganglia, and if so whether or not they are limited to the serosa or mesenteric attachment. This, then, is the dilemma and we may ask whether there is any way to resolve it for the human disease, and if not, how much light can be derived from further studies on experimental animals? Faber and Silverberg [34] have recently attempted to supply the answer to some of these questions by a histopathological study of the peripheral cranial and sympathetic ganglia in fatal human cases. Bodian and Howe [44] in a recent communication on the significance of lesions in peripheral ganglia in chimpanzee and human poliomyelitis have challenged the conclusions of these authors on the basis that the lesions in the sympathetic ganglia could not be regarded as specific for poliomyelitis while those in the craniospinal ganglia in fatal cases or even in the earliest paralytic stage in experimental animals cannot serve as indicators of primary portal of entry, since at that stage they are invariably involved by centrifugal spread of virus from the central nervous system. My own observations [13] lead me to agree with Bodian and Howe [44] in their conclusion that it is not possible to obtain the answer to this particular question from a histopathological study of material from fatal human cases. I do believe, however, that it should be possible to obtain the answer by an extensive, judiciously designed virus assay study on cynomolgus monkeys or chimpanzees sacrificed at various stages after feeding of a strain of virus which would produce paralytic poliomyelitis in them.

The last question I would like to take up in our consideration of the events which follow human infection with poliomyelitis virus is concerned with the distribution and effects of the virus in the subclinical, so-called abortive, nonparalytic, and transitory paralytic forms of the disease. In 1941, unequivocal evidence was published indicating that subclinical or nonparalytic forms of poliomyelitis infection not only existed in monkeys inoculated with strains of recent human origin but that they were associated with neuronal lesions of varying extent in the same centers of the central nervous system which are affected by the virus in the paralytic disease.[46, 47] It was furthermore shown that the virus need not necessarily destroy all the

affected neurons but may produce only partial degenerative changes from which recovery is possible.[46, 46a] Since evidence of extensive neuronal destruction could be found in the spinal cord of monkeys exhibiting no evidence of paralysis, it was apparent that the segmental distribution of the lesions could be of such a nature that there would be no interference with the major innervation of a given muscle. Similarly, it was found that the transitory character of paralysis occasionally observed in monkeys was also on the basis of specific effects on the neurons.[46] In human infection the question remained whether in the many subclinical or mild abortive cases without any physical signs pointing to involvement of the nervous system, there, nevertheless, was such involvement, or whether viral multiplication was limited to the peripheral tissues. In 1945, Bodian and Howe [32] reported that among seven chimpanzees with clinically inapparent or nonparalytic poliomyelitis but excreting virus in their stools, there was none without lesions of some kind in the central nervous system. They stated that because of the great similarity in the response of chimpanzees and human beings to infection with poliomyelitis virus, there was reason to believe that in human beings also, the so-called systemic or peripheral type of inapparent poliomyelitis, with virus restricted to peripheral tissues and ganglia, may be rare or nonexistent. In 1946, I had an opportunity to study an outbreak of poliomyelitis among American marines in Tientsin, China, and found that lumbar punctures had been done on at least 40 men who had only a very mild transitory febrile illness without any detectable nuchal or spinal rigidity; in 25 of these, pleocytosis was present ranging from 50 to 500 cells per cu. mm. During the past summer (1947), Dr. A. J. Steigman and I studied a mild illness of which there were many thousands of cases among the children of Cincinnati, Ohio, and which was generally called "summer grippe" or "summer sore throat." [47a] Among 10 such children, who were representative of thousands that were left at home, we found five with pleocytosis, and from two of the remaining five, without either pleocytosis or nuchal-spinal rigidity, we recovered poliomyelitis virus. In poliomyelitis, pleocytosis results from an overflow of cells from the Virchow-Robin spaces, which to begin with were most probably called forth by some neuronal injury.[48] Nor can it be said that the absence of pleocytosis in the other patients necessarily indicates that the central nervous system was not involved.

The factors which determine the limited multiplication or dissemination of poliomyelitis virus within the central nervous system in those with inapparent or nonparalytic infections are little understood and should provide an important field for future study. That one factor is to be found in the host is evident from the fact that from the central nervous system of nonparalytic monkeys which had successfully halted the infection in the spinal cord or prevented its extension to the spinal cord, it was still possible, several weeks after the acute stage, to recover virus which in other monkeys produced the severe paralytic disease.[46] The extent to which such an equi-

librium or "armed truce" between the virus and the host may exist in human beings who exhibit no signs of infection or only a very mild "summer grippe" or "summer sore throat" is unknown, but that it exists is highly probable. The frequency with which fatiguing exercise or severe exertion may be followed by paralysis after an interval of 24 hours or less in individuals with a history of antecedent minor illness or even without any such history, suggests that the virus was probably already in the central nervous system at the time of the physical stress, and that this provocative factor might have upset the equilibrium between the virus and the host achieved at some earlier time.[46, 49, 49a] Although the question of the existence of strains of poliomyelitis virus with inherently low virulence, irrespective of the status of the host, has often been considered, there has been no conclusive experimental work on it. The fact that strains of very high virulence for the monkey have been recovered from very mild or inapparent human infections has emphasized the rôle of the host. However, during the recent Cincinnati epidemic of so-called "summer sore throat" or "summer grippe," we have found evidence suggesting the operation of strains of poliomyelitis virus of very low virulence for monkeys in many of these minor illnesses, while strains of high virulence for monkeys were recovered from paralytic cases which were occurring at the same time.[47a] Also to be considered in this connection is the growing body of evidence which indicates that there is not just one immunological type of poliomyelitis virus but many. It is not improbable that the antigenic complexity of different strains may be such that in some instances infection with one type may confer no immunity at all against another, while in others there may be a partial immunity which could modify the course of subsequent infection.

In the last part of this discussion, I should like to consider some of the issues which contribute to the uncertainty which still surrounds the question of dissemination of the virus in nature, with special reference to how it reaches the person who will become infected. Although the bulk of the evidence continues to point to man as the primary and chief reservoir of the virus, it is not at all settled, as some would have it, that intimate association with other human beings is the chief and most important means of transmission. First of all what is the present status of the existence in nature of hosts other than man? Leaving out of consideration the unusual circumstances in which a chimpanzee or special breed of monkey may become spontaneously infected, is there any evidence that domestic animals or birds or rodents may be hosts for the virus and sources of human infection? In two recent communications, it was reported by one investigator [50] that three of 37 dog serums in Chicago, and by another group of investigators [51] that 78 per cent of 55 domestic cows, 63 per cent of 48 domestic horses, and 44 per cent of 112 domestic chickens, among other animals tested, neutralized the Lansing mouse-adapted virus. There is no question now that the Lansing mouse-adapted virus represents a *bona fide* human poliomyelitis virus,

immunologically identical with a number of other strains of human poliomyelitis virus and yielding similar results in tests with human sera as were obtained with the monkey strains. Is it possible then to conclude from these reports that like the arthropod-borne encephalitis viruses, poliomyelitis virus can also have a wide host range in nature? My own answer to this question is no. The amount of virus used in the reported tests was so small and the degree of so-called neutralization, therefore, as a rule so slight and so unlike the extensive neutralization produced by the majority of adult human sera, that the results on the animal sera cannot be regarded as specific or indicative of previous infection with poliomyelitis virus. In my own studies with the Lansing virus (in association with Dr. I. Young) it was found that the children on Okinawa developed antibodies for this virus at a very early age, but when eight goats, six horses and nine chickens from the same region were tested against varying amounts of virus, all yielded results which were regarded as negative by comparison with those obtained with the children's sera. Furthermore, Hammon and his associates [51] reported that chickens fed or inoculated with poliomyelitis strains of recent human origin neither excreted virus in the feces nor developed neutralizing antibodies. Also Pearson and his associates [52] have recently reported negative results in their search for virus in the tissues or feces of a large variety of animals present in the environment of human cases of poliomyelitis.

The so-called poliomyelitis-like viruses recovered from rodents, or with the aid of rodents,[53] have added their share of confusion. From a study of all the available data, it is my own considered opinion that the viruses known as MM, FA, GDVII, and related strains are spontaneous encephalomyelitis viruses of rodents, and are no more poliomyelitis-like or related to the poliomyelitis viruses than are the St. Louis, Japanese B, equine and a host of other encephalomyelitis-producing viruses.

The only other creatures from which poliomyelitis virus has been recovered unequivocally in nature, are the nonbiting flies collected in both rural and urban areas during epidemics.[13, 54] The demonstration that flies in an epidemic area can contaminate food with enough virus to transmit the infection to chimpanzees that eat it,[55] has given the nonbiting flies added epidemiologic significance. The recent work of Melnick and Penner [56] strongly suggesting that the flies may not be mere passive carriers but that virus of recent human origin may actually multiply in them and be excreted for three weeks or longer, needs confirmation and extension because of the important bearing it may have on the dissemination of the virus in nature. It may be added here that tests by Hammon,[51] Paul,[54] Francis [52] and their associates on thousands of mosquitoes caught during epidemics of poliomyelitis have all yielded negative results.

Among students of the epidemiology of poliomyelitis there are now three main views on the mode of spread of the disease, all regarding the human being as the primary reservoir of the virus. These views or hypotheses,

for the sake of emphasis, may be called the respiratory, the alimentary, and the alimentary plus the nonbiting flies. The "respiratory" hypothesis postulates that transmission occurs when the virus is breathed out or otherwise expelled from the nose or mouth of one person and is then breathed in by another. The "respiratory" hypothesis is based chiefly on: (1) the demonstrated presence of virus in the pharynx; (2) the conviction, gained from tracing contacts of patients, that the infectious period in poliomyelitis is very short [8, 57] corresponding more to the limited time the virus is present in the throat than to the longer time it is excreted in the stools; and (3) the so-called radial spread of the disease.[57] According to the "alimentary" hypothesis the virus is transmitted by being put into the mouth as by contaminated fingers or food. The "alimentary" hypothesis is based on the following considerations: (1) the stools are the richest potential source of the virus and other infectious agents in excreta are known to be transmitted in a great variety of ways both direct and indirect; (2) the possibility of infection by the oral route has now been established beyond doubt in experiments on animals [13, 31, 33]; (3) studies on other infectious agents have shown that the "nasal" rather than the "pharyngeal" carriers are the "dangerous" carriers,[25] and in the case of poliomyelitis there is no evidence that virus is ordinarily present in the nose [16, 17]; (4) while the virus is present in the pharynx there is no evidence that *under ordinary conditions* it is expelled from the mouth in droplets which could be breathed in by someone else [16, 17]; (5) when virus is breathed in by experimental animals, there is invariably involvement of the olfactory pathway,[58] which is not the case in human beings; (6) "healthy" carriers far outnumber the sick individuals, and the infective period of poliomyelitis cannot definitely be defined as short by tracing contact only to individuals who are sick and therefore largely out of circulation a few days after onset; (7) the phenomenon of radial spread of a human disease can only suggest that the primary reservoir of the infectious agent is in man, and does not indicate one way or another the way it is transmitted.

Neither the "respiratory" nor the "alimentary" hypothesis attempts to account for the fact that 90 per cent or more of the cases and most of the epidemics occur during the late summer and autumn, except for the assumption that hot weather makes the individual more prone to have the paralytic form of the disease. Against this view is the fact that most of the high incidence peaks are in September rather than during the hotter summer months, that when epidemics start late they frequently continue on into October and November, that small epidemics can occur in cold weather, and that the hottest climates have the smallest number of cases with the paralytic form of the disease. The "alimentary plus nonbiting flies" hypothesis regards the predominance of the disease during the late summer and early autumn as being due to greater dissemination of the virus by flies contaminated with infected human excrement. According to this view small

outbreaks can occur in the absence of flies and epidemics can continue at least for a time after the advent of cold weather has caused the flies to disappear, because of the large number of human carriers that are established by the initial widespread dissemination of the virus. The fact that the great improvements in the standards of living and community sanitation during the last half century have instead of lowering the incidence of poliomyelitis tended rather to raise it, and the fact that in the parts of the world where sanitation is of the lowest order and flies in greatest abundance poliomyelitis is a notoriously rare disease, have been brought forward as objections to both "alimentary" hypotheses. Actually, however, there is evidence that in densely populated countries with primitive sanitation poliomyelitis infection is more widespread than elsewhere, although paralytic poliomyelitis which is relatively uncommon among the natives, appears with great frequency among the foreigners in their midst who come from the more hygienic countries,[59] although it is possible that hygiene may have nothing to do with it.

From the point of view of public health practice, it is of considerable importance which of these views is closest to the truth. For according to the "respiratory" hypothesis, you can get the infection without touching anything or anybody or swallowing anything, and the epidemiologic prototype for poliomyelitis is measles and diphtheria. On the other hand, according to the "alimentary" hypothesis you *cannot* get the infection without touching somebody or something contaminated with virus and transferring it with the fingers to the mouth or swallowing food which has been contaminated in any of a great variety of ways. According to the "alimentary plus nonbiting flies" hypothesis intimate person to person contact by itself does not explain the late summer-autumn predominance of the disease, and stresses as an added factor the potential increase in virus dissemination by the nonbiting flies. In both "alimentary" hypotheses the epidemiologic prototype is bacillary dysentery with its inapparent infections, multiple immunologic types, and multiple modes of spread.

I have tried to present to you the available data as critically, and yet as dispassionately, as possible. Nevertheless, I recognize the possibility that I may have overstressed some and understressed others, and that in my limited vision I may have overlooked the truly crucial problems in the natural history of poliomyelitis.

BIBLIOGRAPHY

1. Sabin, A. B., and Ward, R.: The natural history of human poliomyelitis. I. Distribution of virus in nervous and non-nervous tissues, Jr. Exper. Med., 1941, lxxiii, 771–793.
2. Kessel, J. R., Moore, F. J., Stimpert, F. D., and Fisk, R. T.: Occurrence of poliomyelitis virus in autopsies, patients and contacts, Jr. Exper. Med., 1941, lxxiv, 601–609.
3. Sabin, A. B.: The olfactory bulbs in human poliomyelitis, Am. Jr. Dis. Child., 1940, lx, 1313–1318.

4. Howe, H. A., and Bodian, D.: Poliomyelitis in the chimpanzee: a clinical-pathological study, Bull. Johns Hopkins Hosp., 1941, lxix, 149–169; Neuropathological evidence on the portal of entry problem in human poliomyelitis, *ibid.*, 1941, lxix, 183–204.
5. Sabin, A. B.: Pathology and pathogenesis of human poliomyelitis, Jr. Am. Med. Assoc., 1942, cxx, 506–511.
6. Sabin, A. B., and Olitsky, P. K.: The olfactory bulbs in experimental poliomyelitis: their pathologic condition as indicator of portal of entry of virus, Jr. Am. Med. Assoc., 1937, cviii, 21–24.
7. Howe, H. A., and Bodian, D.: Portals of entry of poliomyelitis virus in the chimpanzee, Proc. Soc. Exper. Biol. and Med., 1940, xliii, 718–721.
8. Aycock, W. L., and Kessel, J. F.: The infectious period of poliomyelitis and virus detection, Am. Jr. Med. Sci., 1943, ccv, 454–465.
9. Seddon, H. J., Agius, T., Bernstein, H. G. G., and Tunbridge, R. E.: The poliomyelitis epidemic in Malta 1942–3, Quart. Jr. Med. (N. S.), 1945, xiv, 1–26.
10. McFarlan, A. M., Dick, G. W. A., and Seddon, H. J.: The epidemiology of the 1945 outbreak of poliomyelitis in Mauritius, Quart. Jr. Med. (N. S.), 1946, xv, 183–208.
11. Dauer, C. C.: Incidence of poliomyelitis in 1946, Pub. Health Rep., 1947, lxii, 901–909.
12. Flexner, S.: Respiratory versus gastro-intestinal infection in poliomyelitis, Jr. Exper. Med., 1936, lxiii, 209–226.
13. Sabin, A. B.: Studies on the natural history of poliomyelitis (Bela Schick Lecture), Jr. Mt. Sinai Hosp., 1944, xi, 185–206.
14. Flexner, S., and Amoss, H. L.: Persistence of the virus of poliomyelitis in the nasopharynx, Jr. Exper. Med., 1919, xxix, 379–395.
15. Ward, R., Horstmann, D. M., and Melnick, J. L.: The isolation of poliomyelitis virus from human extraneural sources. IV. Search for virus in blood of patients, Jr. Clin. Invest., 1946, xxv, 284–286.
16. Sabin, A. B., and Ward, R.: The natural history of human poliomyelitis. II. Elimination of the virus, Jr. Exper. Med., 1941, lxxiv, 519–529.
17. Ward, R., and Walters, B.: The elimination of poliomyelitis virus from the human mouth or nose, Bull. Johns Hopkins Hosp., 1947, lxxx, 98–105.
18. Howe, H. A., Bodian, D., and Wenner, H. A.: Further observations on the presence of poliomyelitis virus in the human oropharynx, Bull. Johns Hopkins Hosp., 1945, lxxvi, 19–24.
19. Horstmann, D. M., Melnick, J. L., and Wenner, H. A.: The isolation of poliomyelitis virus from human extraneural sources. I. Comparison of virus content of pharyngeal swabs, oropharyngeal washings, and stools of patients, Jr. Clin. Invest., 1946, xxv, 270–274.
20. Pearson, H. E., and Brown, G. C.: Recovery of virus from throats of poliomyelitis patients, Proc. Soc. Exper. Biol. and Med., 1947, lxvi, 503–505.
21. Wenner, H. A., and Tanner, W. A.: Widespread distribution of poliomyelitis in households attacked by the disease, Proc. Soc. Exper. Biol. and Med., 1947, lxvi, 92–94.
22. Horstmann, D. M., Ward, R., and Melnick, J. L.: The isolation of poliomyelitis virus from human extraneural sources. III. Persistence of virus in stools after acute infection, Jr. Clin. Invest., 1946, xxv, 278–283.
23. Gould, C. W., and Qualls, G. L.: A study of the convalescent carriers of typhoid, Jr. Am. Med. Assoc., 1912, lviii, 542–546.
24. Purjesz, B., and Perl, O.: Über das Vorkommen der Typhusbazillen in der Mandhöhle bei Typhuskranken, Wien. klin. Wchnschr., 1912, xxv, 1494–1495.
25. Hamburger, M., Jr., Green, M. J., and Hamburger, V. G.: The problem of the "dangerous carrier" of hemolytic streptococci. I. Number of hemolytic streptococci expelled by carriers with positive and negative nose cultures, Jr. Infect. Dis., 1945, lxxvii, 68–81; II. Spread of infection by individuals with strongly positive nose cultures who expelled large numbers of hemolytic streptococci, *ibid.*, 1945, lxxvii, 96–108; IV. Ob-

servations upon the role of the hands, of blowing the nose, of sneezing, and of coughing in the dispersal of these microörganisms, *ibid.*, 1946, lxxix, 33–44.

26. Clark, P. F., Roberts, D. J., and Preston, W. S., Jr.: Passage of poliomyelitis virus through the intestinal tract, Jr. Prev. Med., 1932, vi, 47–58.
27. Sabin, A. B., and Ward, R.: Behavior of poliomyelitis virus in cynomolgus monkeys infected by the oral route, Jr. Bact., 1942, xliii, 86–87.
28. Howe, H. A., and Bodian, D.: Attempts to infect African green monkeys by oral administration of poliomyelitis virus, Am. Jr. Hyg., 1947, xlv, 223–225.
29. Faber, H. K., Silverberg, R. J., and Dong, L.: Poliomyelitis in the cynomolgus monkey, Jr. Exper. Med., 1943, lxxviii, 499–526.
30. Howe, H. A.: Personal communication.
31. Howe, H. A., and Bodian, D.: Poliomyelitis in the chimpanzee: a clinical-pathological study, Bull. Johns Hopkins Hosp., 1941, lxix, 149–169.
32. Bodian, D., and Howe, H. A.: Nonparalytic poliomyelitis in the chimpanzee, Jr. Exper. Med., 1945, lxxxi, 255–273.
33. Melnick, J., and Horstmann, D.: Active immunity to poliomyelitis in chimpanzees following subclinical infection, Jr. Exper. Med., 1947, lxxxv, 287–303.
34. Faber, H. K., and Silverberg, R. J.: A neuropathological study of acute poliomyelitis with special reference to the initial lesion and to various potential portals of entry, Jr. Exper. Med., 1946, lxxxiii, 329–353.
35. Trask, J. D., and Paul, J. R.: Intracutaneous inoculation of poliomyelitis virus in monkeys and its detection in their stools, Ann. Int. Med., 1942, xvii, 975–978.
36. Melnick, J. L.: Recovery of poliomyelitis virus from the stools of experimentally infected monkeys and chimpanzees, Jr. Immunol., 1946, liii, 277–290.
37. Sabin, A. B., and Ward, R.: The natural history of experimental poliomyelitis. I. Studies on the centrifugal spread and elimination of the virus in intrasciatically inoculated monkeys, Jr. Exper. Med., 1944, lxxv, 107–117.
38. Howe, H. A., and Bodian, D.: Poliomyelitis by accidental contagion in the chimpanzee, Jr. Exper. Med., 1944, lxxx, 383–390.
39. Melnick, J. L.: Poliomyelitis virus in the blood stream in the experimental disease, Proc. Soc. Exper. Biol. and Med., 1945, lviii, 14–16.
40. Peck, J. L., and Sabin, A. B.: Multiplication and spread of the virus of St. Louis encephalitis in mice with special emphasis on its fate in the alimentary tract, Jr. Exper. Med., 1947, lxxxv, 647–662.
41. Sabin, A. B.: Experimental poliomyelitis by the tonsillopharyngeal route, Jr. Am. Med. Assoc., 1938, cxi, 605–610.
42. Aycock, W. L., and Luther, E. H.: Occurrence of poliomyelitis following tonsillectomy, New Eng. Jr. Med., 1929, cc, 164–167.
43. Anderson, J. A.: Poliomyelitis and recent tonsillectomy, Jr. Pediat., 1945, xxvii, 68–70.
44. Bodian, D., and Howe, A.: Significance of lesions in peripheral ganglia in chimpanzee and in human poliomyelitis, Jr. Exper. Med., 1947, lxxxv, 231–242.
45. Bodian, D.: Experimental evidence on the cerebral origin of muscle spasticity in acute poliomyelitis, Proc. Soc. Exper. Biol. and Med., 1946, lxi, 170–175; Poliomyelitis: neuropathologic observations in relation to motor symptoms, Jr. Am. Med. Assoc., 1947, cxxxiv, 1148–1154.
46. Sabin, A. B., and Ward, R.: Nature of nonparalytic and transitory paralytic poliomyelitis in rhesus monkeys inoculated with human virus, Jr. Exper. Med., 1941, lxxiii, 757–770.

46a. Bodian, D.: The virus, the nerve cell, and paralysis, Bull. Johns Hopkins Hosp., 1948, lxxxiii, 1–107.

47. Bodian, D., and Howe, H. A.: The pathology of early arrested and nonparalytic poliomyelitis, Bull. Johns Hopkins Hosp., 1941, lxix, 135–146.

47a. Sabin, A. B., and Steigman, A. J.: Poliomyelitis virus of low virulence in patients with epidemic "summer grippe or sore throat," Am. Jr. Hyg., 1949, in press.

48. Bodian, D., and Howe, H. A.: Experimental studies on intraneural spread of poliomyelitis virus, Bull. Johns Hopkins Hosp., 1941, lxviii, 248–264.

49. Levinson, S. O., Milzer, A., and Lewin, P.: Effect of fatigue, chilling and mechanical trauma on resistance to experimental poliomyelitis, Am. Jr. Hyg., 1945, xlii, 204–213.

49a. Russell, W. R.: Poliomyelitis: The preparalytic stage, and the effect of physical activity on the severity of paralysis, British Med. Jr., 1947, ii, 1023–1028.

50. Gordon, F. B.: The neutralization of poliomyelitis virus by dog serums, Jr. Infect. Dis., lxxvi, 198–202.

51. Hammon, W. McD., Mack, W. N., and Reeves, W. C.: The significance of protection tests with the serum of monkeys and other animals against the Lansing strain of poliomyelitis virus, Jr. Immunol., 1947, lvii, 285–299.

52. Pearson, H. E., et al.: Studies of the distribution of poliomyelitis virus. I. In the environment of sporadic cases, Am. Jr. Hyg., 1945, xli, 164–178; II. In a small town, *ibid.*, 1945, xli, 179–187; III. In an urban area during an epidemic, *ibid.*, 1945, xli, 188–210.

53. Jungeblut, C. W., and Dalldorf, G.: Epidemiological and experimental observations on possible significance of rodents in suburban epidemics of poliomyelitis, Am. Jr. Pub. Health, 1943, xxxiii, 169–172; Epidemiological and experimental observations of poliomyelitis in New York (1943–1944), Am. Jr. Hyg., 1946, xliii, 49–64.

54. Paul, J. R., Trask, J. D., Bishop, M. B., and Melnick, J. L.: The detection of poliomyelitis virus in flies, Science, 1941, xciv, 395–396; The detection of poliomyelitis virus in flies collected during epidemics of poliomyelitis, Jr. Exper. Med., 1943, lxxvii, 531–556.

Sabin, A. B., and Ward, R.: Flies as carriers of poliomyelitis virus in urban epidemics, Science, 1941, xciv, 590–591; Insects as carriers of poliomyelitis virus, *ibid.*, 1942, xcv, 169–170.

Melnick, J. L., and Ward, R.: Susceptibility of vervet monkeys to poliomyelitis virus in flies collected at epidemics, Jr. Infect. Dis., 1945, lxxvii, 249–252.

55. Ward, R., Melnick, J. L., and Horstmann, D. M.: Poliomyelitis virus in fly-contaminated food collected at an epidemic, Science, 1945, ci, 491–493.

56. Melnick, J. L., and Penner, L. R.: Experimental infection of flies with human poliomyelitis virus, Proc. Soc. Exper. Biol. and Med., 1947, lxv, 342–346; also personal communication of unpublished data.

57. Casey, A. E.: Place of contact and radial spread of epidemic poliomyelitis, Am. Jr. Dis. Child., 1945, lxix, 152–156.

58. Faber, H. K., Silverberg, R. J., and Dong, L.: Poliomyelitis in the cynomolgus monkey, Jr. Exper. Med., 1944, lxxx, 39–57.

59. Sabin, A. B.: Epidemiology of poliomyelitis: problems at home and among the armed forces abroad, Jr. Am. Med. Assoc., 1947, cxxxiv, 749–756.

ANDROGEN THERAPY *

By W. O. Thompson, M.D., F.A.C.P., *Chicago, Illinois*

Introduction

Many substances with androgenic properties have been isolated from the testes, adrenals, blood, and urine, but the most potent androgenic material isolated so far is testosterone. This substance was isolated from the testis by Laqueur and his colleagues in 1935 [1] and was synthesized in the same year by Ruzicka [2] and Butenandt.[3] Various observations suggest that it is more potent when administered in the form of an ester than when given in the free form. In clinical medicine it is usually administered in the form of the propionate.

Although other androgens have been isolated and prepared synthetically, they are rarely used in clinical medicine and a discussion of androgen therapy is, therefore, concerned primarily with the effects of testosterone.

There is still some debate as to what the male sex hormone actually is, although many observers have considered it to be testosterone in active chemical combination. The functions of other androgens in the body have not been clearly determined, although they may play some rôle in metabolism. For example, the adrenal cortex produces various androgenic materials but we do not know just what their functions in the body are, and in particular whether or not they are normally concerned with the development and maintenance of secondary sex characteristics. Tumors of the adrenal cortex sometimes develop which produce a great excess of androgen, especially dehydroisoandrosterone. In young boys these tumors cause precocious puberty and in sexually mature women cause masculinization, characterized by amenorrhea, atrophy of the breasts, enlargement of the clitoris, hirsutism, lowering of the pitch of the voice, and acne.

Some of the androgenic material isolated from urine comes from the adrenal cortex and the adrenal cortex continues to produce androgenic material after castration.[4] However, the adrenal cortex seems to be unable to substitute for the testis after castration and does not prevent the development of all the signs and symptoms of eunuchism.

Functions of Androgens

Androgens and estrogens should be looked upon not merely as materials which stimulate sex function, but as general metabolic stimulants which influence the function of all tissues in the body. This point of view can readily

* Read at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 21, 1948.

From the Department of Medicine, University of Illinois College of Medicine and the Grant and Henrotin Hospitals, Chicago.

be appreciated by a consideration of the functions of the sex hormones. The male sex hormone is responsible for the development of the secondary sex characteristics of the male, which include [5]:

1. Growth of the external genitalia.
2. Growth and function of the prostate gland.
3. Increase in the size and firmness of the muscles.
4. Masculine distribution of hair.
5. Lowering of the pitch of the voice.
6. Normal configuration of the skeleton.
7. Normal emotional reactions.

Its influence on the development of the musculature and the skeleton, and on the emotional status of the individual is evidence of its general metabolic effect. During normal puberty the musculature of the male increases in size and firmness. The same changes are observed when puberty is induced with chorionic gonadotropin or testosterone. The quality of the musculature of the male depends on various factors, which include heredity, nutrition, and hormones. An adequate quantity of male sex hormone is essential for the skeleton to attain normal proportions. If it is absent during puberty, the trunk becomes short in proportion to the extremities, the shoulders narrow, and the hips broad. Because of the influence of the male sex hormone on calcium metabolism, its administration has been suggested to promote healing of bone in older men with fractures. The male sex hormone also promotes retention of nitrogen in the body and influences the metabolism of various electrolytes, including sodium and chloride. When administered in large quantities it will cause pitting edema of dependent portions of the body. A very common effect of its administration is the production of acne. It exercises a profound influence on the emotional reactions of men.

Sexually immature men usually have a sense of inferiority and go to great lengths to cover up their physical defect. They also may suffer from depression and have suicidal ideas. When the male sex hormone is suddenly withdrawn from a normal man by castration, similar emotional disturbances may result, as well as atrophy of the genitalia, loss of hair from various parts of the body, decrease in muscle strength, weakness, lack of ability to concentrate and hot flashes.

Types of Hypogonadism

In order to carry out androgen therapy intelligently, it is necessary to have a clear understanding of the various types of hypogonadism. The testis has two functioning parts, namely, the seminiferous tubules which produce spermatozoa, and the interstitial cells of Leydig, which produce male sex hormone.[6, 7] The functions of these two portions of the testis are interrelated and normal spermatogenesis appears to be in part dependent upon normal production of male sex hormone. However, these functions may

vary independently and the testis may show atrophy of the seminiferous tubules without much impairment of function of the interstitial cells.

It has been suggested by some observers, including Törnblom [8] and McCullagh,[9] that the testis produces a second hormone which is estrogenic in nature and is elaborated by the seminiferous tubules.

There is a close relation between the anterior lobe of the pituitary and the testis. The anterior lobe of the pituitary produces a follicle-stimulating hormone which influences the function of the seminiferous tubules and a luteinizing hormone which stimulates the interstitial cells to produce male sex hormone. Hypogonadism may therefore be either primary or secondary, the primary type being caused by some defect in the testis itself, and the secondary type being the result of some defect in the stimulating mechanism in the pituitary. These two types of hypogonadism, on theoretical grounds, may be further subdivided as follows:

PRIMARY TYPE

1. Hypofunction of the seminiferous tubules without impairment of the interstitial cells.
2. Hypofunction of the interstitial cells without impairment of the function of the seminiferous tubules.
3. Hypofunction of both portions of the testis.

SECONDARY TYPE

1. Deficient production of follicle-stimulating hormone, affecting primarily the seminiferous tubules.
2. Defective production of luteinizing hormone, affecting primarily the interstitial cells.
3. Defective production of both follicle-stimulating and luteinizing hormones, affecting the function of both portions of the testis.

Theoretically, all of these types of hypogonadism may be present, but in most instances when there is a deficient function of one portion of the testis, there is some evidence of a deficient function of the other. It is not uncommon to observe atrophy of the seminiferous tubules and azoospermia in men whose testes produce enough male sex hormone to maintain secondary sex characteristics. The opposite of this condition, namely, normal function of the seminiferous tubules with deficient function of the interstitial cells is theoretically possible, but has rarely been observed.

STIMULATION AND SUBSTITUTION THERAPY

Androgen therapy is substitution therapy whereas gonadotropic therapy is stimulation therapy.[5] Androgens should be employed when it is impossible to stimulate the testis adequately with gonadotropins. Chorionic gonadotropin is a very effective material for stimulation of the interstitial cells of the testis, but does not have much influence on the function of the seminiferous tubules. Pituitary and equine gonadotropins theoretically

stimulate the functions of both portions of the testis, but primarily the function of the seminiferous tubules, because they contain an excess of follicle-stimulating hormone. In actual practice they are not very effective, and we therefore do not have any satisfactory method of stimulating spermatogenesis when it is deficient.

Uses of Androgens

Androgen therapy appears to be of value in the following conditions[6]:

1. Eunuchism.
2. Primary eunuchoidism.
3. Bilateral intra-abdominal cryptorchism.
4. The Fröhlich syndrome associated with intra-abdominal cryptorchism.
5. Pituitary dwarfism.
6. Carcinoma of the breast.
7. Functional uterine bleeding.
8. Suppression of lactation.
9. Impotence from glandular causes.
10. The male climacteric.
11. Fractures in old men.
12. Cushing's syndrome.
13. Addison's disease.
14. Hypopituitarism with secondary hypogonadism in old men.

Eunuchism

In eunuchism there is complete loss of all functions of the testis as a result of removal, injury, or atrophy. The intramuscular administration of testosterone propionate in oil usually substitutes completely for the male sex hormone. The effects of its administration depend somewhat upon the age at which treatment is carried out. If an individual is castrated during childhood, the administration of testosterone propionate during the age of puberty will cause normal development of the secondary sex characteristics, including growth of the genitalia, development of the musculature, normal configuration of the skeleton, lowering of the pitch of the voice and growth of hair on the body.

If an individual is castrated during childhood and treatment is delayed until after the age of puberty, some skeletal disproportion persists and the genitalia, musculature, and hair cannot be made to develop as much as if the stimulus is applied during the age of puberty. Testosterone propionate is effective throughout life, and even if treatment is delayed until the age of 60 years, a considerable amount of development of secondary sex characteristics can be induced. The ideal age to begin treatment in eunuchs is 11 or 12 years. The defect is a permanent one and such individuals require treatment throughout life. The amount of material required to produce maximum

development varies in different patients but in many, maximum development can be induced with 25.0 mg. given intramuscularly three times a week. In some instances as much as 50.0 mg. a day may be necessary.

When men are castrated after the age of puberty, the administration of testosterone propionate will restore the secondary sex characteristics to normal.

Primary Eunuchoidism

In eunuchoidism there is only partial loss of testicular function. There is always a deficient production of male sex hormone, and almost always a deficient function of the seminiferous tubules. It may be associated with bilateral cryptorchism or atrophic testes may be present in the scrotum. Whether it is primary or secondary in nature can be determined by an assay of the follicle-stimulating hormone in the urine. If this is present in normal or increased quantities, it may be assumed that the primary defect is in the testis and that the function of the pituitary is normal. If it is present in deficient amounts, it may be assumed that the primary defect is in the pituitary and that the testis is not properly stimulated.

If facilities for hormone assays are not available, the type of eunuchoidism may be determined by the administration of chorionic gonadotropin. If the testis responds to stimulation therapy it may be assumed that the eunuchoidism is of the secondary type; and, if it does not respond, that it is of the primary type. It is a good general rule to observe the effect of stimulation therapy before resorting to substitution therapy with androgens. In many patients with eunuchoidism, after the age of puberty, the testis may show a definite response to stimulation therapy with chorionic gonadotropin, but may not produce enough male sex hormone to cause adequate development of the secondary sex characteristics. Under these circumstances treatment with testosterone propionate may be desirable even though the eunuchoidism is of the secondary type. It is possible that in these patients irreparable damage to the testes occurs as a result of the long period of absence of adequate stimulation.

The treatment of the eunuchoid state should be started at the age at which puberty normally begins, namely, 11 or 12 years. If the testes are in the scrotum it is not always easy to be certain at this early age that the function is deficient, and for this reason treatment is often delayed until irreparable changes in the skeleton and musculature occur. In eunuchoid individuals the testes are usually abnormally small even before puberty. When the testes are in the abdominal cavity, an effort should be made to bring them into the scrotum by treatment with chorionic gonadotropin or testosterone propionate. The actual type of treatment used depends upon whether or not the testes can respond to stimulation therapy. After the testes have been brought into the scrotum, further treatment may be delayed until the age of puberty.

It is recommended that the testes be brought into the scrotum as early as possible because they cannot function normally in the abdominal cavity and after they have been brought into the scrotum they may be able to respond more readily to stimulation therapy. The risk of permanent damage to the testes appears to be greater the longer they remain in the abnormal environment of the abdomen.[10]

Bilateral Intra-Abdominal Undescended Testes

In most patients with undescended testes, chorionic gonadotropin is the best therapeutic agent. It may produce definite stimulation of genital growth even when both testes are in the abdominal cavity. This material should, therefore, be used first and the administration of testosterone propionate resorted to only if chorionic gonadotropin is ineffective. In some instances intra-abdominal testes will descend into the scrotum with glandular therapy, but very often surgical measures are necessary after some stimulation of genital growth has been produced with chorionic gonadotropin or testosterone propionate.

The Fröhlich Syndrome and Undescended Testes

In most patients with the Fröhlich syndrome the testes are in the scrotum, but they are undescended in patients with this disorder more commonly than in normal individuals. In patients with the Fröhlich syndrome in whom both testes are in the abdominal cavity, treatment with chorionic gonadotropin should be tried first and testosterone propionate used if it is ineffective.

Patients with bilateral intra-abdominal cryptorchism may have hypogonadism of the primary or secondary type and the cryptorchism may be caused by mechanical or glandular factors. If the testes fail to function properly when they are brought into the scrotum, glandular therapy of the stimulation or substitution type must be continued indefinitely, the form of therapy depending upon the type of hypogonadism which is present. The dose of chorionic gonadotropin required varies from patient to patient, but in most instances the intramuscular administration of 500 I. U. of this material three times a week is adequate. The dose of testosterone propionate that is required also varies from patient to patient, but in most instances 25.0 mg. administered intramuscularly three times a week will cause complete development of secondary sex characteristics.

Pituitary Dwarfism

Testosterone propionate is a very potent stimulator of genital growth. When androgens are present in large quantities in young boys, either as the result of tumors of the adrenal or testis, or as the result of therapeutic administration, they cause rapid growth of the skeleton in length and affect the skeletal proportions. Young boys with tumors of the adrenal cortex, which

produce an excess of androgens, grow rapidly in height and for a few years are taller than most boys of their age. Eventually they become somewhat short in stature because of the premature closure of their epiphyses. The administration of chorionic gonadotropin, which stimulates the testes to produce androgenic material, also causes rapid growth in height in young boys.

Because of its growth promoting properties, testosterone propionate is of definite value in the treatment of pituitary dwarfism. It stimulates that component of growth associated with puberty, but is not a substitute for the growth hormone of the pituitary or for the thyroid hormone, without which the skeleton cannot become normal in length. In other words, the pituitary dwarf who is treated with testosterone propionate at the proper age, grows taller and develops proper proportions between various parts of his skeleton. The maximum amount of growth in height which we have observed during the administration of this material to a pituitary dwarf is ten inches. The individual remains a dwarf, but does derive the benefit of the growth that is associated with the onset of sexual maturity. The growth promoting properties of testosterone propionate are of great practical importance because of the fact that there is no effective preparation of the growth hormone of the pituitary available at the present time. The stimulation of genital growth in pituitary dwarfs is necessary only when there is deficient production of pituitary gonadotropins, as well as of pituitary growth factor, and the treatment should be started at the age at which puberty usually gets under way, namely, at the age of about 12 years.

The hypogonadism associated with hypopituitarism is of the secondary type and the administration of chorionic gonadotropin is, therefore, usually effective in stimulating skeletal growth in pituitary dwarfs. Testosterone propionate needs to be used only when a maximum effect cannot be produced with chorionic gonadotropin.

Carcinoma of the Breast

There have been two very interesting developments in the relation of hormones to cancer. These developments concern carcinoma of the prostate and carcinoma of the breast. A few years ago Huggins [4, 11] reported that surgical castration and functional castration with stilbestrol produced a very striking improvement in patients with carcinoma of the prostate. The lesion in the prostate diminished in size, the metastases in bone became calcified, and, in some instances, the roentgen-ray evidence of metastases disappeared. There was an associated disappearance of pain and great improvement in the general nutritional state of the individual. Of the original 20 patients reported by Huggins, four were alive six years after surgical castration and showed no evidence of metastases.

In many patients, following initial improvement, relapse was noted and they proceeded to die of cancer of the prostate. To explain this phenomenon, Huggins [4] has suggested that the cancer cells, in many in-

stances, take on androgen independence and that, while androgenic material may be necessary initially for the growth of the cancer cells, they eventually become independent of this stimulation. These observations are of great interest, but it is obvious that androgen stimulation alone will not result in the development of cancer of the prostate. Some factor must be present in the cells themselves, which makes them undergo malignant degeneration under the influence of this stimulus.

The hormonal status in cancer of the breast is similar to that in cancer of the prostate.[12, 13, 14, 15, 16] Many years ago it was noted that women with cancer of the breast often showed some improvement following removal of the ovaries. Recently it has been observed that the administration of testosterone propionate in large doses causes definite amelioration of symptoms in patients with this disorder. It does not have much effect on the lesion in the breast, but seems to be effective in bone metastases, regardless of the age of the patient. It causes some calcification of the metastases, causes the pain to disappear, and improves the nutritional status of the patient. The mechanism of this action in older people is not easy to understand. In women before the age of the menopause, it could be considered the result of suppression of ovarian function. For some reason which is not clear at the present time, estrogenic therapy causes a diminution in the local lesion in the breast and in soft tissue metastases in women after the age of the menopause. This effect is not easy to understand if the development of carcinoma of the breast is the result of estrogenic stimulation, but there does not appear to be much doubt about the fact that improvement occurs with this type of treatment in older women. On the other hand, estrogenic therapy is said to be contraindicated in women with carcinoma of the breast before the age of the menopause. The improvement which follows glandular therapy in women with carcinoma of the breast is less striking than the improvement which follows glandular therapy in men with cancer of the prostate and most patients, after initial improvement, die of carcinoma of the breast. The dose of testosterone propionate required to produce improvement is approximately 100 mg. three times a week. This amount of material is given over a period of eight to ten weeks, following which smaller amounts of material may be used. Androgenic therapy in these doses produces some masculinization, but masculinization can be tolerated provided the symptoms of cancer are ameliorated and life expectancy increased. It should be emphasized that glandular therapy is indicated only in the treatment of inoperable cancer of the breast. The treatment of choice in all patients with operable carcinoma is radical mastectomy.

Functional Uterine Bleeding

It is generally agreed that the administration of testosterone propionate is of definite value in controlling functional uterine bleeding. Before resorting to such treatment the patient must be carefully examined in order to make

sure that the bleeding is functional in origin. Tumors and other anatomic abnormalities in the uterus and blood dyscrasias must be excluded. It is very desirable to use the smallest amount of material that will control the bleeding, in order not to cause masculinization. Methyltestosterone may be given by mouth. The effective dose varies from patient to patient. It is claimed that women will tolerate as much as 300 mg. of methyltestosterone per month without undergoing masculinization.

Suppression of Lactation

It has been reported that androgenic therapy is of value in suppressing lactation following childbirth. Similar improvement has also been claimed as a result of the administration of various estrogens. It is thought that both androgenic and estrogenic material influence lactation by suppressing pituitary function. As in the case of functional uterine bleeding, it is very important to use small amounts of testosterone so that masculinization will be avoided.

Impotence from Glandular Causes

Impotence associated with definite hypogonadism is promptly relieved by the administration of testosterone propionate or chorionic gonadotropin, the form of treatment depending upon whether the hypogonadism is primary or secondary in type. In many patients impotence is neurogenic or psychogenic in origin and is not corrected by glandular therapy. If adequate laboratory facilities are available for hormone assays, it is possible to determine whether hypogonadism is present or not. If such facilities are not available, stimulation or substitution therapy may be tried, according to the type of hypogonadism which appears to be present. If improvement occurs it usually means that the impotence is associated with a glandular deficiency. Occasionally patients in whom there is an important neurogenic or psychogenic factor will show some improvement with glandular therapy.

The Male Climacteric

There is a great deal of debate as to whether or not there is such a disorder as the male climacteric. There is no definite epoch in the male like the menopause in the female, and climacteric changes are certainly much less common in the male than in the female. However, there appears to be little doubt that in some men a definite decrease in the production of androgenic material occurs as they grow older and that this decrease is sufficient to produce symptoms which are similar to those observed in the menopause of the female and include hot flashes, ease of fatigue, irritability, palpitation and depression. These changes are often associated with an increase in the secretion of follicle-stimulating hormone in the urine, although the laboratory evidence for the diagnosis of the male climacteric is not very clear cut.

Great caution should be exercised in making the diagnosis and it should be arrived at only after the most careful examination of the patient and after every other possible cause for the symptoms has been excluded. When the condition definitely exists the administration of testosterone propionate in a dose of 25.0 mg. intramuscularly three times a week causes amelioration of the symptoms.

Fractures in Old Men

Because of the influence of testosterone propionate on the growth of bone and on the deposition of calcium in bone, the administration of this material may be of value in old men with fractures. A sufficient number of observations have not been made to prove the efficacy of this form of treatment beyond doubt, but a few observations have been made by reliable investigators. Similar improvement has been reported in older women with fractures as a result of the administration of estrogenic material, which also influences the growth of bone.

Cushing's Syndrome

In some patients with Cushing's syndrome there is an excessive loss of nitrogen in the urine and under these circumstances the administration of testosterone propionate may be of value because it promotes retention of nitrogen. It does not cure the disease, but in some instances may produce a great deal of improvement temporarily.

Addison's Disease

The administration of androgenic material has been recommended in the treatment of Addison's disease in both the male and female. In Addison's disease the adrenal cortex is usually completely destroyed and this source of androgenic material in the body is therefore lost. We have not observed its effect in the female but, in our experience, in the male the administration of testosterone propionate, in addition to specific therapy, often produces more improvement than specific therapy alone.

Hypopituitarism with Secondary Hypogonadism in Old Men

In most patients with hypogonadism secondary to hypopituitarism, chorionic gonadotropin is the material of choice for the correction of the hypogonadism. In older men the testis does not respond as well to stimulation therapy and the administration of testosterone propionate is indicated.

Misuses of Androgenic Therapy

The administration of testosterone propionate is either contraindicated or of no value in the following conditions:

1. Sterility.
2. Benign prostatic hypertrophy.

3. Carcinoma of the prostate.
4. The Fröhlich syndrome with one or both testes in the scrotum.
5. Undescended testes, unless there is no response to stimulation therapy with chorionic gonadotropin.
6. Impotence, if not glandular in origin.
7. Arteriosclerotic or hypertensive heart disease in old men.

In large doses testosterone propionate may depress testicular function and cause an actual azoospermia. In moderate doses it does not appear to have this effect and may have a beneficial effect on spermatogenesis. In most instances it is of little value in stimulating spermatogenesis in sterile men.

Testosterone propionate has been reported to produce some improvement in men with benign prostatic hypertrophy, but careful search for objective signs of improvement by several investigators has resulted in the conclusion that it is of little or no value. The male sex hormone is responsible for the development of the prostate and it is difficult to see how the administration of this material would reduce its size. It may possibly in some instances produce a little improvement by increasing the tone of the muscle of the bladder.

In view of the possible rôle which androgens may play in the development of carcinoma of the prostate, it is unwise to administer androgens to any man who is suspected of having this disorder.

The status of glandular therapy in the Fröhlich syndrome, undescended testes, and impotence has already been discussed.

In old men with arteriosclerotic and hypertensive heart disease, androgen therapy may increase the risk of a vascular accident by increasing muscle activity. The danger is not very great, but should always be borne in mind.

Conditions in Which Androgenic Therapy Is of Doubtful Value

1. Angina pectoris.
2. Homosexuality.
3. Dysmenorrhea.
4. Carcinoma of the ovaries.

Lesser [17] reported definite improvement in about 50 per cent of the patients with angina pectoris following the administration of testosterone propionate. The improvement appeared about six to eight weeks after the administration of the material was started. Other reports have appeared concerning the use of this material in angina pectoris, but the evidence of improvement is not convincing.

Glandular therapy has not proved very effective in the treatment of homosexuality. Testosterone has been administered intramuscularly in large doses to homosexual men without improvement in most instances. Occasionally slight improvement occurs, but the results on the whole are dis-

appointing. Negative results have also been obtained with the use of estrogenic therapy in homosexual females. Sometimes the administration of stilbestrol to homosexual males will reduce their interest in members of the same sex, by suppression of testicular function. Estrogenic therapy must be administered cautiously to males because of its feminizing effects, including enlargement of the breasts.

The administration of testosterone propionate has been reported to be beneficial in some women with dysmenorrhea. The data are not extensive enough to warrant definite conclusions. Estrogenic material has also been reported to produce improvement and would certainly be the material of choice because of the risk of inducing masculinization with androgenic therapy. Dysmenorrhea is a complicated disturbance and involves neurogenic and psychogenic factors, as well as glandular factors.

Androgenic therapy has also been recommended in the treatment of afterpains and engorgement of the breasts. It may be of some value in reducing engorgement of the breasts following childbirth, but it has not been tried on a sufficiently large scale in these two conditions to justify any conclusions concerning its value.

Harmful Effects of Androgen Therapy

1. Injury to the normal testis, with production of azoospermia.
2. Acne vulgaris.
3. Masculinization in women.
4. Pitting edema of the lower legs.
5. Hypermetabolism.

Injury to the Normal Testis. The administration of large doses of testosterone propionate, such as 50.0 mg. per day, may produce an azoospermia in a man with a normal spermatozoa count. Histologically, there is a striking effect on the seminiferous tubules. Following the omission of treatment the seminiferous tubules recover and the spermatozoa count returns to normal. It has not been demonstrated whether or not permanent damage can be produced by the prolonged administration of large doses. In moderate doses, such as 25.0 mg. three times a week given intramuscularly, testosterone propionate does not appear to reduce the spermatozoa count, and in small doses may actually have a beneficial influence on spermatogenesis because of the close relationship that exists between the functions of the two portions of the testis.

Acne Vulgaris. The administration of testosterone propionate to men or boys commonly causes acne, the extent of which depends upon the size of the dose and some individual susceptibility of the skin of the patient. Acne can also be produced in young boys by the administration of chorionic gonadotropin, which stimulates the production of male sex hormone. Acne appears without treatment at puberty when the production of androgenic material increases. There seems to be little doubt that there is a close cor-

relation between the concentration of androgenic material in the body and the development of acne vulgaris.

Masculinization in Women. As already pointed out, the administration of testosterone propionate in fairly large doses produces masculinizing effects in women, which include lowering of the pitch of the voice, development of hair in masculine areas, atrophy of the breasts, amenorrhea, decrease in vaginal secretion, and enlargement of the clitoris. These effects are undesirable and whenever androgenic therapy is indicated in the female, every effort should be made to employ a dose which does not produce them. Masculinizing effects cannot be avoided in the treatment of women with inoperable carcinoma of the breast.

Pitting Edema of the Lower Legs. Testosterone propionate promotes retention of nitrogen, sodium, and chloride, and when given in large doses often causes pitting edema in the lower legs. In moderate doses, which are adequate to induce sexual maturity in immature men, namely, 25.0 mg. three times a week, it usually does not produce this effect.

Hypermetabolism. During the administration of 50.0 mg. of testosterone propionate daily by intramuscular injection, the basal metabolism may rise as much as 35 to 40 per cent above normal. The administration of methyltestosterone by mouth in large doses will also cause a striking rise in basal metabolism. The mechanism of this action is not known, and in particular, it is not known whether it is the result of a direct effect on the metabolism of tissues or whether it is the result of some action on the pituitary or thyroid. Individuals who show an increase in metabolism during androgenic therapy do not present symptoms suggestive of hyperthyroidism. In doses of 25.0 mg. three times a week the basal metabolism is usually not affected.

Methods of Administration

Testosterone may be administered in the following ways:

1. Intramuscularly in the form of testosterone propionate.
2. Subcutaneously in the form of pellets.
3. Intramuscularly as a suspension of free testosterone in water.
4. By mouth in the form of methyltestosterone.

For the production of maximum changes the intramuscular administration of testosterone propionate appears to be most effective. Pellets have not been used very extensively and further work should be done in order to determine whether or not they will produce maximum masculinizing effects. They may be of value for maintenance therapy after maximum changes have been induced by the intramuscular administration of testosterone propionate. Free testosterone suspended in water is of value when administered intramuscularly, but there are not enough data to state the relative effectiveness of this method of treatment, as compared with the intramuscular administration of testosterone propionate. Methyltestos-

terone produces a definite effect when administered by mouth, but is not as effective as testosterone propionate given intramuscularly. Like pellets, it may be of value for maintenance therapy.

Summary

This article presents a resumé of the uses, misuses, and harmful effects of androgenic therapy, and a discussion of the conditions in which androgen therapy is of doubtful value.

Bibliography

1. Laqueur, E., David, K., Dingemanse, E., and Freud, J.: Ueber Männliches Hormon: Unterschied von Androsteron aus Harn und Testosteron aus Testis, Acta brev. Neerland, 1935, v, 84.
2. Ruzicka, L., Wettstein, A., and Kägi, H.: Sexual Hormone: VIII. Darstellung von Testosteron unter Anwendung gemischter Ester, Helvet chim. Acta, 1935, xviii, 1478.
3. Butenandt, A., and Hanisch, G.: Ueber Testosteron: Umwandlung des Dehydroandrosterons in Androstendiol und Testosteron; ein Weg zur Darstellung des Testosterons aus Cholesterin, Ztschr. f. physiol. Chem., 1935, ccxxxvii, 89.
4. Huggins, C.: Prostatic cancer treated by orchiectomy: five year results, Jr. Am. Med. Assoc., 1946, cxxxi, 576.
5. Thompson, W. O., and Heckel, N. J.: Male sex hormone, clinical application, Jr. Am. Med. Assoc., 1939, cxiii, 2124.
6. Thompson, W. O.: Uses and abuses of the male sex hormone, Jr. Am. Med. Assoc., 1946, cxxxii, 185.
7. Moore, C. R.: Physiology of the testis, *in* Glandular Physiology and Therapy, 1942, American Medical Association, Chicago.
8. Törnblom, N.: Internal secretion of the germinal tissue of the testes and prostatic hypertrophy, Upsala läkaref. förh., 1942, xlviii, 1.
9. McCullagh, D. R.: Dual endocrine activity of the testes, Science, 1932, lxxvi, 19.
10. Thompson, W. O., and Heckel, N. J.: Undescended testes. Present status of glandular treatment, Jr. Am. Med. Assoc., 1939, cxii, 397.
11. Huggins, C.: Endocrine control of prostatic cancer, Science, 1943, xcvii, 541.
12. Herrmann, J. B., and Adair, F. E.: Effect of testosterone propionate on carcinoma of female breast with soft tissue metastases, Jr. Clin. Endocrinol., 1946, vi, 769.
13. Schwander, H., and Marvin, H. N.: Treatment of carcinoma of human breast with testosterone propionate: report of five cases, Jr. Clin. Endocrinol., 1947, vii, 423.
14. Report of a Subcommittee of the Therapeutic Trials Committee of the Council on Pharmacology and Chemistry of the A.M.A.: Estrogens and androgens in mammary cancer, Jr. Am. Med. Assoc., 1947, cxxxv, 987.
15. Snapper, I.: Castration combined with testosterone treatment after mastectomy for breast cancer: endocrinologic and metabolic changes, Jr. Mt. Sinai Hosp., 1947, xiv, 618.
16. Ayre, J. E.: Cervical cancer: disordered growth response to inflammation in presence of estrogen excess and nutritional deficiency, Am. Jr. Obst. and Gynec., 1947, liv, 363.
17. Lesser, M. A.: Testosterone and propionate therapy in 100 cases of angina pectoris, Jr. Clin. Endocrinol., 1946, vi, 549.

THE PHYSIOLOGIC EFFECTS OF PHYSICAL THERAPY *

By George Morris Piersol, M.D., M.A.C.P., *Philadelphia, Pennsylvania*

During the past 10 years interest in physical medicine has increased markedly. In spite of this physicians continue to show considerable scepticism as to the advantages of this form of therapy. This attitude is due in no small measure to the belief that physical medicine does not rest upon a sound physiological basis. The purpose of the following remarks is to point out that the most useful and commonly employed procedures in physical medicine, i.e. the use of various forms of heat and cold, massage, and therapeutic exercise, depend for their effectiveness upon well established physiological reactions. A thorough understanding of these reactions is as essential to the successful use of physical therapy as is correct diagnosis, accurate anatomic knowledge of the involved part, and familiarity with various technics.

Heat

Heat, in some form, applied generally or locally, represents the therapeutic measure most frequently used in any department of physical medicine. A summary of one year's experience in a general hospital showed that of 23,345 treatments given in the department of physical medicine heat was a feature in 44.3 per cent of cases. Next to heat came massage, 34 per cent, and then therapeutic exercise, 15.4 per cent. The value of heat in the management of many conditions, based upon clinical observation, appears to be well established. In spite of the widespread employment of heat as a therapeutic agent and extensive physiological studies on the effects of heating, the complex changes that are induced when human beings are subjected to heat are still imperfectly understood. Their solution awaits further investigation.

Briefly it may be stated that the most important effect of the systemic application of external heat is to increase body temperature. Regardless of the method employed the fever thus produced is the result of creating a disproportion between heat production and heat dissipation. The degree to which temperatures may thus be elevated depends upon the duration and amount of heat energy input and the efficiency with which output is controlled. Phenomena which accompany the induction of fever consist of an increase in pulse and circulatory rates. According to Krusen and Elkins,[1] both the volume output of the heart and the velocity of the blood may be increased up to 400 per cent. Marked peripheral vasodilatation occurs. The

* Presented before the General Session of the American College of Physicians at San Francisco, California, April 22, 1948.

From the Center for Instruction and Research in Physical Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia 4, Pennsylvania.

respiration is accelerated. The rise in temperature is usually associated with sweating. When this is profuse and not offset by adequate fluid administration, reduction in blood volume occurs which may be sufficient to bring about peripheral vascular failure. Dehydration and hyperventilation induce alkalosis which at times reaches a critical level. There are no significant changes in either the nitrogenous or non-nitrogenous constituents of the blood, except that with profuse sweating the blood chlorides are decreased. The red cell count is altered but little. After the febrile reaction is established the leukocyte count rises and there is a relative increase in neutrophiles and decrease in lymphocytes.[2] Hartman [3] has pointed out that a serious effect of induced fever may be anoxemia. The value of prolonged hyperthermia in combating certain infections (notably luetic and gonococcal) depends upon the bactericidal effect of the fever as well as the stimulation of the defense mechanisms of the body against disease.

Observations recently carried out by Horvath and Botelho at the University of Pennsylvania furnish data on some physiological reactions that are brought about when individuals are placed under the abnormal stress of heat, regardless of whether it is used in its positive aspect, as a hot bath, or in its negative aspect, as a cold bath.

They employed 19 subjects, seven males and 12 females. Their average age was 28 years and all of them were in excellent physical condition. After a control period of rest during which repeated observations were made on heart rate, blood pressure and cardiac output, the subject was immersed to the neck for 20 minutes in a tank of water maintained at a temperature of either 18° C. or 40° C. Heart rates were obtained every minute, blood pressure every two minutes during the immersion. After removal from the bath the subject was observed for at least 20 minutes and in some instances for one hour. Cardiac output, heart rate and blood pressure were again repeatedly recorded. Oral and rectal temperatures were taken immediately and 30 minutes after the bath.

Twenty-two experiments were conducted on 17 subjects with hot baths. The observers found that the body temperature rises appreciably following immersion in a bath of 40° C., namely 37.6° to 38.4° or a mean increase of 0.8° C. This is a rate increase of 2.4° C. per hour. Oral temperatures in general showed a similar rise. A half hour after removal from the bath the rectal temperatures were still elevated and in a few individuals it had not returned to normal levels for over an hour.

During the bath the heart rate was increased in the first minute after immersion. At the end of 20 minutes it was approximately 50 per cent greater than the control level. As a result of a lower diastolic pressure pulse pressure also increased. Immediately after the hot bath the heart rate began to return to normal, although it required some 20 minutes before control levels were attained. Cardiac output one minute after the bath was found to be increased in all subjects, the average rise being 42 per cent.

Fourteen minutes after the bath cardiac output in eight subjects had returned to normal, but it was still elevated in the remaining subjects as much as 40 per cent. This increased cardiac output was associated with rapid heart rate, in some instances double the control value. It was concluded that the increased cardiac output was primarily due to the higher heart rate, since the average stroke volume did not differ from control values.

Only 11 subjects were available for exposure to baths of 18° C. Shivering occurred in all but one case. The rectal temperature dropped on an average of 0.1° C. during the bath. The shivering, a defense reaction, was doubtless a factor in maintaining the level of heat production. A more significant drop in temperature occurred a half hour after removal from the cold bath. At this time in all subjects it fell at least 0.2° C. below the values obtained immediately after the bath. After the first half hour body temperature began to return to control levels.

The first two minutes after immersion in cold water the systolic pressure rose rapidly, the result of initial vaso-constriction. At this time shortness of breath was also marked. Following these early changes subjects were able to relax and systolic blood pressure returned to approximately control values, although the heart rate continued to rise. During the post-bath observation period there was a slowing of the heart rate. In the first minute after the 18° C. exposure cardiac output was reduced. Fourteen minutes later it was below control values in all subjects, showing an average decrease of 10 per cent.

Since the thermal stimuli used in these experiments were so mild that the organism was able to make and maintain adequate adjustments, Horvath concluded the degree of stress induced could be more completely evaluated if individuals were subjected to an added stress-producing stimulus. Change in posture was, therefore, imposed upon the stimulus of the hot or cold bath. Position was changed alternately from supine to erect passively by means of a tilting ballistocardiograph. In each position heart rate and blood pressure and cardiac output were measured. After these pre-bath observations the subject was immersed to the neck for twenty minutes in a bath with a temperature of either 18° C. or 40° C. Upon completion of the bath the subject was returned to the ballistocardiograph and observed through two supine and two erect periods in the same manner as during the control period.

Approximately one-half of the subjects developed orthostatic hypotension following immersion for 20 minutes in a bath of 40° C. Based upon the post-thermal orthostatic responses they divided their subjects into three groups: (1) the syncopal, (2) the abnormal, and (3) the normal. The syncopal group included four individuals who, when upright, developed typical symptoms and signs of syncope of varying intensity. No evidences of syncope or distress were observed after the hot bath in any individual while kept supine.

Ten subjects were subjected to postural stress after being exposed to the cold bath. The only difference in response observed was that in erect position after the bath the increase in heart rate was only minor compared with that noted from the pre-bath or control tilt.

These observations on the effects of hot baths, especially when they are combined with postural change, furnish an explanation for the not infrequent occurrence of syncope after prolonged hot baths. They further emphasize the importance of a period of rest in the recumbent position following exposure of the body to unaccustomed prolonged heating.

The local application of heat continues to be one of the most readily available procedures in physical therapy. The commonest methods of applying heat are by conduction, when an exchange of molecular energy is brought about by direct contact and by convection, when the source of heat is hot water, hot air, or the infra-red radiant energy derived from lamps or reflectors. All of these forms of heating are relatively inefficient and slow and their penetration slight. The radiant energy produced in the near infra-red range is the most penetrating and produces some rise in temperature of the subcutaneous tissue after prolonged exposure.

An effective procedure which raises the temperature of the deeper tissues is the conversion of alternating electric currents of high frequency into heat. This method of heat production is referred to as short wave diathermy. Either a condensor field or an induction field can be employed in the production of heat by short wave diathermy.

Under ordinary conditions the physiological effects brought about by the local application of heat, regardless of the method employed, consist of increased local circulation characterized by vaso-dilatation, a rise in capillary pressure, acceleration of the transfer of fluid from the blood to the tissues and an increase in local metabolic activity and probably phagocytosis. As a rule, an excessive concentration of heat in the tissues is prevented by increased blood flow which distributes the heat throughout the body. However, recent experimental work on the rate of blood flow in animals treated with short wave diathermy raises some doubt as to whether this mechanism is operative under such conditions.

Mart and Miller [4] measured the rate of blood flow through the coronary vessels before, during and after the application of short wave diathermy over the heart and noted no significant increase in the flow of blood. Kemp, Paul and Hines [5] found that the femoral arterial inflow into the hind leg of dogs was reduced when the limb was treated with diathermy. This reduction was noted whether the limb treated was denervated or not denervated. Heretofore it has been generally stated that diathermy causes an increase of blood flow in the deeper structures. From these observations the thought arises that, since such is apparently not the case, at least in part some of the rise in temperature of the deeper structures that is induced by diathermy is due to a decrease in the flow of blood to the heated tissue.

In the course of a discussion of the physiological effects of heat Horvath [6] states that two factors must always be considered in heat therapy, (1) the amount of heat successfully applied into the tissues, and (2) the extra amount of heat produced in the tissue as a consequence of the oxidation processes that have been accelerated by the heat applied. These factors deserve careful consideration when heat therapy is contemplated.

The realization of the importance of this principle brought about a radical change in attitude towards the use of heat in patients suffering from impaired peripheral circulation. All forms of heat in even moderate degree are dangerous to ischemic limbs. When arterial flow is obstructed, or even diminished, exposure to even mild temperatures of from 80° to 90° F. can cause an increase in metabolism which demands more oxygen than is available when arterial flow is inadequate. Thus a relative ischemia develops which induces increased pain and leads to edema, ulceration and gangrene. When vasodilatation in an extremity is desirable, reflex dilatation of vascular channels may be brought about by heating some other part of the body and thus avoiding disturbance of the metabolism of the affected extremity. This was demonstrated by Landis and Gibbons.[7] Intact sympathetic innervation of the part is essential if this procedure is to be effective.

The same principle applies when obstructive lesions of the venous circulation are present. With the arterial channels open the demand for additional blood created by heating can be met. However, with the venous return flow impaired adequate cooling and heat dissipation are so interfered with that the temperature of the tissue rises to levels which bring about edema and ulceration. It is in these peripheral vascular lesions that cooling and even mild refrigeration, which tend to lessen circulatory demands and diminish metabolic activity, have proved a more effective form of physical therapy than heat.

In certain inflammatory conditions, notably the more acute stages of arthritis or trauma such as sprains and fractures in their early stages when frank or latent edema is present, it is a common clinical observation that the local application of heat, and especially the deep heating induced by diathermy, aggravates the pain and swelling. The explanation is that, if heat locally increases tissue fluid exchange, the already present tissue fluid accumulation is increased to the point where pressure on the venous channels and lymphatics interferes with the return circulation.

Ordinary methods of applying heat therapeutically are slow and ineffective in raising deep tissue temperatures. Short wave diathermy alone is capable of bringing about deep heating with any degree of rapidity. In order to meet the need for some method of causing rapid, deep, localized heating of tissue there has recently been developed a device by which human tissue may be heated by microwave radiation. The instrument generates energy in a continuous wave, air-cooled, magnetron oscillator tube which operates at a frequency of 2400 to 2500 megacycles or at a wave length of

approximately 12 cm., with a maximum power output of 125 watts. It will be recalled that the development of the magnetron oscillator tube made possible radar, which played such an important part during the war. Now its usefulness has been extended to the field of medicine.

At the direction of the Council on Physical Medicine of the American Medical Association the new apparatus has been investigated by Stafford L. Osborne and Jesse N. Fredericks of the Department of Physical Medicine and Physiology of Northwestern University Medical School.[8]

Of the several investigations that are being carried out on the effects of the high frequency current of this magnitude on human beings, those of Horvath, Miller and Hutt of the Department of Physical Medicine, University of Pennsylvania, will be discussed.[9]

These investigators have studied nine subjects, six males and three females, varying in age from the early twenties to the late sixties. In order to measure the deep and superficial tissue temperatures, needle thermocouples were inserted into the thigh. Temperature readings were recorded at the surface, at a depth of 4 to 13 mm. in the subcutaneous tissue, and in muscle at a depth of 30 mm. or over. Control observations were made before the application of the radiation. Thermocouples were then removed from the area to be treated. Immediately after a 15 or 30 minute exposure in the radiation field of a microwave generator with a magnetron tube oscillating at a frequency of 2450 megacycles per second and a wave length of 12.2 cm., thermocouples were replaced and the cooling of tissues was observed for a period varying from 30 to 130 minutes. A power output of 50 watts was used most often because of the frequency with which this dosage has been employed in clinical trials of this mode of therapy.

The application of this form of high frequency, electrical energy caused no discomfort to the patients treated, who reported only a pleasant sense of warmth and were not conscious of the high internal temperatures developed. The lack of subjective discomfort presents a certain element of danger because it leads patients, as well as operators, to believe that only a small amount of heat is being generated and creates the desire to increase the power output which might well bring about serious effects on the deep tissues.

The findings of Horvath and his associates in general correspond to the results that have been obtained by Krusen, Herrick, Leden and Wakim[10] and Osborne and Fredericks.[11] Horvath's summary is as follows: "The employment of high frequency electrical energy in a 12 centimeter band (2450 megacycles per second of the electro-magnetic spectrum) provides a means of selectively heating local masses of tissue. The magnitude and depth of heating may be altered by varying directors and the power output of the generator. Maximal temperatures observed following a 15 minute period of heating, utilizing a power output of 50 watts with a six-inch director, were 36.4° C. at the surface, 44° C. at subcutaneous levels and 40° C. in muscle tissue. In the majority of experiments the temperature gradient from sub-

cutaneous tissue to muscle to surface was not modified greatly as a consequence of this mode of heating. However, in a large number of instances the subcutaneous and muscle gradient was reversed. High internal temperatures were secured with only incidental elevation of surface temperatures. No increase in rectal temperatures was observed."

At the present time Horvath et al. are studying the effects of microwave on blood flow. Krusen and others have reported a definite increase in the circulation of the heated extremity in both experimental and clinical study. Much careful clinical observation must be carried out before the therapeutic value and harmlessness of the microwave on human beings is firmly established.

In recent years no subject in physical medicine has evoked more discussion and controversy than the use of hot packs in the treatment of acute and subacute poliomyelitis. In spite of the extensive use of this now popular procedure, there is an amazing paucity of accurate data on the physiological effects of hot packs. As has been too often the case with other procedures in physical medicine, conclusions in regard to the effects of hot packs have been based largely upon poorly controlled clinical impressions and observations unsubstantiated by experimental findings.

It is of interest, therefore, that Hall and his associates [12] carried out a well planned study of the strength of muscle contractions after hot woolen packs were applied to the overlying skin of the gastrocnemius muscle of etherized cats. They found that so long as the afferent and sympathetic pathways are intact, the application of hot packs commonly though not invariably, causes slowly developing reduction in the strength of muscle contraction. This effect does not occur when the skin over the muscle is anesthetized. From these experiments the authors suggest that hot packs produce their effects by stimulation of cutaneous receptors which, through some reflex mechanism not entirely clear, reduces the strength of muscular contraction. This result does not occur when reflex effects are excluded.

They observed the greatest decrease in muscle contraction occurred when the subcutaneous temperatures averaged between 46° C. and 48° C. They used deep muscle temperatures as the criteria for blood flow in muscle.

Their conclusion is that hot packs stimulate cutaneous receptors which reflexly evoke vaso-constriction and a reduction in blood flow in the muscles and that this is responsible for the impairment of contraction strength. They go on to state that the present assumption, quite generally accepted, that the application of moist heat "always improves the circulation of the underlying structure" will have to be abandoned if further work confirms their findings that reflex vasoconstriction and consequent decrease in muscular strength can be brought about to a significant degree in human muscles by the application of hot packs. They also suggest that the demonstration of increased mobility of joints and the decreased muscle resistance in stretching following treatment by hot packs may indicate not the removal of the cause of the

muscle hypertonia but weakness of the contracture power of the involved muscle.

It is admittedly dangerous to transfer the results obtained on animal experiments to man. From an anesthetized cat to the child with poliomyelitis is a far cry. Nevertheless, the above mentioned experimental observations are suggestive, although their confirmation must await extensive careful studies on human beings. Should this occur, we may be forced to the conclusion that the results now attributed to hot packs may be brought about by other methods that are less time consuming and costly.

From the foregoing remarks on the effects of heat it may be noted that water in all of its forms and because of its physical properties is frequently employed as the medium for applying thermal stimuli. It seems superfluous, therefore, to discuss the physiological effects of hydrotherapy as such. The effectiveness of most forms of hydrotherapy is dependent largely upon the temperature changes induced. It should be pointed out, however, that some forms of hydrotherapy, especially sprays and douches, combine the effects of mechanical stimulation with those due to alteration of temperature.

There is another physical property of water which has been successfully taken advantage of in physical therapy. When a body is immersed in a liquid there is exerted upon it an upward force which is equal in magnitude to the weight of the liquid which that body has displaced. This law, long ago propounded by Archimedes, is the basis of underwater exercise and manipulation. Since the sustaining power of water almost completely carries the weight of the body, it is possible for weakened muscles and diseased joints to carry out motion under water with little or no discomfort which is virtually impossible to accomplish out of water where the force of gravity must be overcome.

Mechano-Therapy

Under mechano-therapy are included massage, therapeutic manipulation and all kinds of exercise. In spite of careful studies that have been carried out by such investigators as Pemberton,[13] Coulter,[14] Mennell,[15] and others, much remains to be done to bring about a complete understanding of the physiological effects of massage.

Massage differs from active motor stimulation in that the acidosis that occurs with active exercise is not present. Contrary to the effects brought about by the application of external heat, massage does not induce the loss of carbonic and lactic acid with resultant alkalosis. Krogh [16] has demonstrated that the most important effect of massage upon the circulation is the change brought about in the capillary bed. From direct observation on the capillaries it has been shown that massage causes an increased rate of blood flow and changes in the vessel wall which result in an increased interchange of substances between the blood and the tissue cells and consequent improvement in metabolism. The mechanical effect of massage in stimulating the

return flow of venous blood and lymph to the heart is a well recognized phenomenon.

Massage stimulates the contraction of both voluntary and involuntary muscles. Various reflex phenomena result from the stimulation of sensory receptors in the skin as well as in the deeper nerve trunks. With the application of external pressure it is possible to displace the contents of hollow viscera and of accessible glands and their ducts. Collections of inflammatory exudate in skin and muscles may be dissipated by massage. As pointed out by Scull,[17] massage involves the application of the stimulus of pressure to tissues. It has been shown that in normal subjects massage has no significant effect on pulse rate, blood pressure or oxygen consumption.

Therapeutic Exercise

The interest of the physiatrist centers chiefly about corrective exercise, which has been defined as the scientific application of bodily movements in the treatment of disease or malfunction. The subject has attained increasing importance of late because of the prominent rôle which remedial exercise plays in the extensive reconditioning programs now established by various agencies throughout the country. Therapeutic exercise has as its primary purpose not so much the development of muscle power, but rather the acquisition of ability to use muscles effectively in carrying out essential acts and skills.

In spite of the enormous amount of work that has been devoted to the changes incident to muscular contraction, there is still considerable divergence of opinion among competent students of the subject.

Systematic muscular exercise brings about changes in the muscles as well as in the body as a whole. As a result of repeated contractions circulation and chemical activities are stimulated which causes increased muscle size. Exercise brings about hypertrophy of muscle fibers but no increase in their number. This results in gain in muscle power. Systematic exercise is frequently referred to by the term "training." Training not only increases muscle power but facilitates the transmission of nerve impulses across the myo-neural junction, thus allowing more muscle fibers to go into action simultaneously. The precision, endurance and coördination that are developed by systematic training enable an individual to perform movements that require great effort at a minimum energy cost.

An assessment of the working capacity of patients suffering from orthopedic handicaps such as those resulting from poliomyelitis and the mutilations of war and industry is of great practical importance. Steindler[18] investigated the energy cost of walking in patients handicapped from infantile paralysis. Thirteen patients, aged six to 20 years, showed an increase in energy expenditure which ranged from 60.8 per cent to 150.8 per cent above normal. Simons and Keyes[19] compared the energy cost of walking on a treadmill of two subjects who had had poliomyelitis with two nor-

mal controls. One of their subjects was clinically entirely recovered from paralysis. The other suffered almost complete atrophy of the right leg which required braces when walking. In the first case they found that his energy expenditure coincided with normal values in all variations in speed and grade up to 3 m.p.h. with a slight tendency to higher values at 4 m.p.h. The second subject when walking with braces exceeded normal values by 1.5 to 2.6 times in all variations investigated. Without braces this individual's energy expenditure was considerably higher. Respiratory efficiency was definitely lower than that of the patient recovered from paralysis. This work suggests the practical value of evaluating the working capacity of persons with orthopedic handicaps.

The physiological fact that the redevelopment of muscle power, even in markedly atrophied muscles, depends upon high resistive, low repetition exercises led DeLorme [20] to devise a system of heavy resistive exercises. For this purpose he has designed a series of weights which can be attached to various parts of the body so that they can be lifted by voluntary muscular effort. According to his program, one day each week the patient exerts maximal power to lift a suitable weight once. On the other days he lifts a weight which is no heavier than that which is maximum for 10 repetitions. Striking results in improved muscle power have been obtained by this procedure.

Hellebrandt [21] and her associates confirmed an older observation that unilateral heavy resistive exercise not only increases the strength of the exercised limb but brings about a similar concomitant effect on the contralateral unexercised limb. They found that the determining factor in this so-called cross education was the amount of effort expended rather than the duration of the exercise. This cross education may prove a useful therapeutic tool in cases in which voluntary control is unilaterally defective or in which contra-lateral muscle groups are temporarily inaccessible because of immobilization.

It is impossible at this time to do more than point out certain of the physiological effects of the most frequently used procedures in physical therapy. It is hoped that the evidence presented in the foregoing remarks has shown that physical therapy actually is applied physiology. Many basic problems await solution, however, before all of the physiological reactions associated with this broad field of therapeutics are well understood and its procedures satisfactorily standardized.

BIBLIOGRAPHY

1. Krusen, F. H., and Elkins, E. C.: Handbook of Physical Medicine, 1945, Am. Med. Assoc., Chicago, Ill., p. 44.
2. Krusen, F. H.: Blood picture before and after fever therapy by physical means, Am. Jr. Med. Sci., 1937, cxciii, 470.
3. Hartman, F. W.: Lesions of brain following fever therapy, Jr. Am. Med. Assoc., 1937, cix, 2116.

4. Mart, J. A., and Miller, J. R.: Effects of diathermy on coronary flow, Am. Heart Jr., 1945, xxix, 390.
5. Kemp, C. R., Paul, W. D., and Hines, H. M.: Studies on blood flow and the efficacy of deep tissue thermogenic agents, Federation Proc., 1947, vi, 141.
6. Horvath, S. M.: Fundamentals of physical medicine of interest to general practitioners, Jr. Am. Med. Assoc., 1948, cxxvi, 605.
7. Landis, E. M., and Gibbons, J. H., Jr.: Simple method of producing vasodilatation in lower extremities, with reference to its usefulness in studies of peripheral vascular disease, Arch. Int. Med., 1933, lii, 785.
8. Osborne, S. L., and Fredericks, J. N.: Report to Council on Physical Medicine, Am. Med. Assoc., 1947, Nov. 28.
9. Horvath, S. M., Miller, R. N., and Hutt, B. K.: The heating of human tissue by microwave radiation, Am. Jr. Med. Sci., 1948, ccxvi, 430.
10. Krusen, F. H., Herrick, J. E., Leden, U. M., and Wakim, K. G.: Microkymatotherapy; preliminary report of experimental studies of heating effect of microwaves ("radar") in living tissues, Proc. Staff Meet., Mayo Clinic, 1947, xxii, 209.
11. Osborne, S. L., and Fredericks, J. N.: Report to Council on Physical Medicine, Am. Med. Assoc., 1947, Nov. 28.
12. Hall, V. E., Munoz, E., and Fitch, B.: Reduction of the strength of muscle contraction by application of moist heat to the overlying skin, Arch. Phys. Med., 1947, xxviii, 493.
13. Pemberton, R.: Principles and Practice of Physical Therapy, 1934, W. F. Prior Co., Inc., Hagerstown, Md., vol. I, chap. 16.
14. Coulter, J. F.: Cyclopedia of Medicine, Surgery and Specialties, 1944, F. A. Davis Co., Philadelphia, Pa., vol. 8, p. 5.
15. Mennell, J. B.: Physical Treatment by Movement, Manipulation and Massage, 1947, The Blakiston Co., Philadelphia, Pa., p. 61.
16. Krogh, M.: Anatomy and Physiology of the Capillaries, 2nd edition, 1929, Yale University Press, New Haven, Conn.
17. Scull, C. W.: Massage—physiologic basis, Arch. Phys. Med., 1945, xxvi, 159.
18. Steindler, A.: Locomotor mechanics and occupation, Trans. Am. Soc. Mechanical Eng., 1945, lxvii, 167.
19. Simons, E., and Keyes, A.: Working capacity in patients with orthopedic handicaps from poliomyelitis; energy expenditure in walking at various speeds and grades, Am. Jr. Physiol., 1947, cli, 405.
20. DeLorme, T. L.: Heavy resistance exercises, Arch. Phys. Med., 1946, xxvii, 607.
21. Duvall, E. N., Houtz, S. J., and Hellebrandt, F. A.: Reliability of a single effort muscle test, Arch. Phys. Med., 1947, xxviii, 213.

THE USE OF THE ANTICOAGULANTS IN THE TREATMENT OF DISEASES OF THE HEART AND BLOOD VESSELS*

By IRVING S. WRIGHT, M.D., F.A.C.P., *New York, N. Y.*

THE TREATMENT AND PROPHYLAXIS OF THROMBOPHLEBITIS AND PULMONARY EMBOLISM

THE first group of diseases to be attacked by means of anticoagulant therapy was quite logically those loosely classified under the broad term of thrombophlebitis, which includes so-called "phlebothrombosis." That this attack has been remarkably successful, though not without some difficulties, is clearly demonstrated by the experiences reported from many workers in this country and abroad.

The significance of this problem is established by the figures compiled by Jorpes from large clinics in widely scattered portions of the world (table 1) (quoted from Zilliacus [1]).

TABLE I

	Cases of Thrombosis	Pulmonary Embolism		Fatal Pul. Embolism	
		Cases	%	Cases	%
	Surgical Cases				
Schneidegg, Singer et al.	1,550	746	48.1	298	19.2
Barker et al.	1,665	897	53.8	343	20.6
Linde et al.	1,230	740	60.1	166	13.5
	Obstetrical Cases				
Holzmann et al.	749	119	15.8	26	3.47
Hellsten	420	150	35.8	20	4.76

Courtesy of Dr. J. Erik Jorpes

Thus it is clearly shown that among post-operative patients who develop venous thrombosis and are treated conventionally, there is a minimal risk† approximating 50 per cent, of pulmonary embolization and that among those patients who have one pulmonary embolism, approximately one-fifth will die of a pulmonary embolism. Physicians are just awakening to the gravity of these figures. The profound effect of anticoagulant therapy, using either

* Presented before the General Sessions of the American College of Physicians, San Francisco, April 23, 1948.

† This is minimal since these figures are based on emboli with infarctions recognized clinically. Autopsy findings indicate that there are large numbers of pulmonary emboli which are never recognized clinically.

heparin or dicumarol, on these statistics has been irrefutably demonstrated by the reports of Allen, Barker and their co-workers [2, 3] (table 2), Zilliacus, Jorpes, Bauer et al. (table 3) of the Scandinavian group, and the previously reported experiences from our own group, and others.[4, 5]

It has also been established that the prophylactic use of anticoagulants post-operatively will decrease the incidence of thrombophlebitis and of pulmonary embolism (table 4).[2, 6, 7]

TABLE II

Effects of Anticoagulants in the Treatment of Postoperative Thromboembolic Complications (Barker, Hines, Kvale, Allen)

	Therapy	
Thrombophlebitis (352)	Conventional	Anticoagulant
Subsequent Thromboembolism	25.3%	2.8%
Fatal embolism	5.7%	0.0%
One Pulmonary Embolism or Infarction (329)		
Subsequent thromboembolism	43.8%	1.0%
Fatal embolism	18.3%	0.3%

TABLE III

Cases of Thrombosis or Pulmonary Infarct (Bauer, Zilliacus)

			Death	Per Cent
Conservative treatment	543		88	16
Heparin	769	900	3	4
Dicumarol	131		1	0.45

Courtesy of Dr. J. Erik Jorpes

TABLE IV

Prophylactic Uses of Dicumarol

Allen, E. V., et al., Mayo Clinic	832 Cases Hysterectomy	
Venous thrombosis or Pulmonary embolism	Anticipated with conventional therapy 33	Occurred with dicumarol 3*
Fatal pul. embolism	6	0
Allen, A. W., and Donaldson, G., Mass. Gen. Hosp.	500 General Surgery	
Fatal pul. embolism	6	0

* Minor small veins.

CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

It was natural that following the early encouraging results in the treatment and prophylaxis of thrombophlebitis interested workers would try this approach in other thrombo-embolic syndromes. Beginning in May 1942, therefore, we treated a series of patients suffering from coronary thrombosis with myocardial infarction. Forty-six of these patients were classified as "complicated" in that they had developed either serial episodes of coronary thrombosis, or secondary embolic accidents or both. The first preliminary

report of our experiences with this new approach was presented in this city (San Francisco) in October 1945 before the California Heart Association.[8, 9, 10] Meanwhile others, notably Nichol and Page,[11] and Peters, Guyther, and Brambel [12] had been pursuing the same approach and also published encouraging results. All of these studies were in reality preliminary, exploratory, and they lacked sufficient numbers of cases or adequate control series.

In the summer of 1946, therefore, under the Auspices of the American Heart Association and with the financial support of the U. S. Public Health Service, a study was set up involving some 16 coöperating hospitals well known for their cardiac services. From each of these hospitals a responsible investigator was appointed to the Committee for the Evaluation of the Use of Anticoagulants in the Treatment of Coronary Thrombosis. Each responsible investigator in turn developed his own research team to coöperate with the Central Laboratory Group located in our laboratory at the New York Hospital. Statistical master forms were developed for compilation of data regarding the cases. During the past 20 months patients admitted to the participating cardiac services on even days of the month have received conventional treatment while those admitted on odd days of the month have received conventional plus anticoagulant treatment.

COMMITTEE FOR THE EVALUATION OF ANTICOAGULANTS IN THE TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION—AMERICAN HEART ASSOCIATION

Participating Hospital	*Responsible Investigators*
Bellevue Hospital, New York	John E. Deitrick, M.D.
Beth Israel Hospital, Boston	Herrman L. Blumbart, M.D.
Bronx Veterans Hospital	Louis A. Kapp, M.D.
Cincinnati General Hospital	Johnson McGuire, M.D. Helen Glueck, M.D.
Cleveland City Hospital	Roy W. Scott, M.D.
Henry Ford Hospital, Detroit	F. Janney Smith, M.D.
Jackson Memorial Hospital, Miami	E. Sterling Nichol, M.D.
Lakeside Hospital, Cleveland	Joseph Hayman, Jr., M.D.
Massachusetts General Hospital	Howard B. Sprague, M.D.
Michael Reese Hospital, Chicago	Louis N. Katz, M.D.
Mount Zion Hospital, San Francisco	John J. Sampson, M.D.
Pennsylvania Hospital, Philadelphia	Joseph B. Vander Veer, M.D.
Peter Bent Brigham Hospital	Samuel A. Levine, M.D.
Rhode Island Hospital, Providence	Frank B. Cutts, M.D.
San Francisco County Hospital	John J. Sampson, M.D.
The New York Hospital, New York	Irving S. Wright, M.D. Harold J. Stewart, M.D.
Consultants	
Ralph S. Overman, Ph.D.	Nelson W. Barker, M.D.
Charles E. Brambel, Ph.D.	Grace Goldsmith, M.D.

Central Laboratory

Irving S. Wright, M.D., Chairman of Study
Charles D. Marple, M.D., Coördinator
Dorothy F. Beck, Ph.D., Statistician

The series has now reached its goal of 1000 alternate cases but because of the necessary lag in statistical analysis, I am able to report to you on the pre-

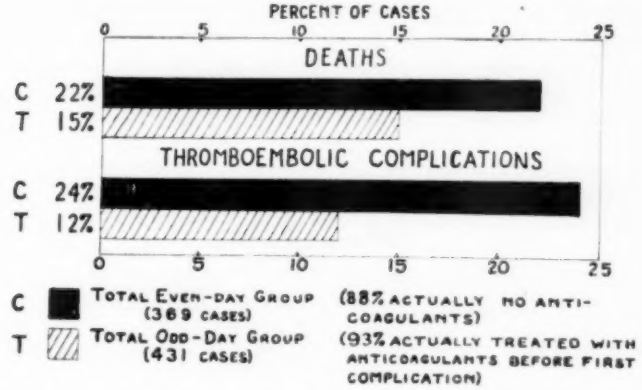

PERCENT OF CASES
0 5 10 15 20 25
DEATHS
C 22%
T 15%
THROMBOEMBOLIC COMPLICATIONS
C 24%
T 12%
0 5 10 15 20 25
C TOTAL EVEN-DAY GROUP (369 CASES) (88% ACTUALLY NO ANTICOAGULANTS)
T TOTAL ODD-DAY GROUP (431 CASES) (93% ACTUALLY TREATED WITH ANTICOAGULANTS BEFORE FIRST COMPLICATION)

CHART I. Anticoagulants in coronary occlusion with myocardial infarction (800 cases).

liminary crude data derived from only 800 cases. Chart 1 represents the total number of patients classified for statistical purposes as "Even day (control group) patients" and "Odd day (anticoagulant treated) patients." It will be noted that actually 12 per cent of the "Control group" did at some time receive some anticoagulants. This was due to (1) error or (2) pressure from family or other sources after patient had become desperately ill. Seven per cent of the "Treated Group" did not receive anticoagulants before the first complication. This was due to (1) delay in admission, (2) delay in diagnosis, (3) contraindications to use of anticoagulants. Chart 2 offers a comparison of the results obtained with those patients treated solely by means of usual or conventional methods and those who in addition actually received

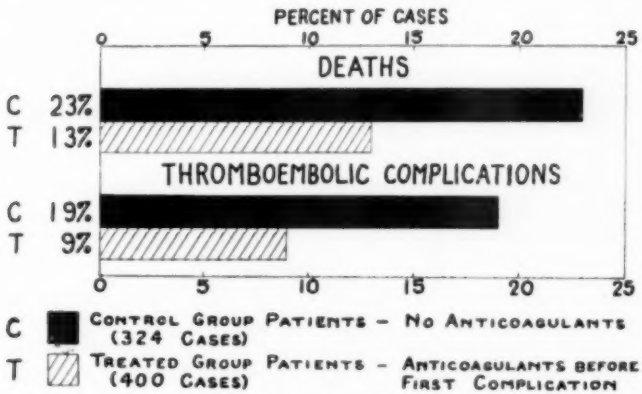

PERCENT OF CASES
0 5 10 15 20 25
DEATHS
C 23%
T 13%
THROMBOEMBOLIC COMPLICATIONS
C 19%
T 9%
0 5 10 15 20 25
C CONTROL GROUP PATIENTS – NO ANTICOAGULANTS (324 CASES)
T TREATED GROUP PATIENTS – ANTICOAGULANTS BEFORE FIRST COMPLICATION (400 CASES)

CHART II. Anticoagulants in coronary occlusion with myocardial infarction (800 cases).

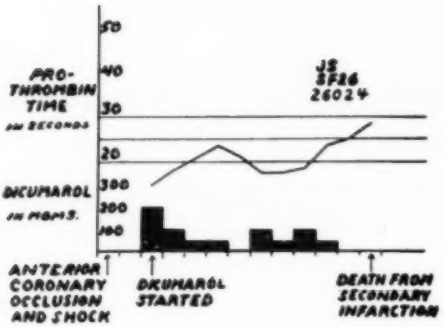


CHART III. Failure with the use of anticoagulant therapy—Note that the therapeutic level of 30 seconds was never reached.

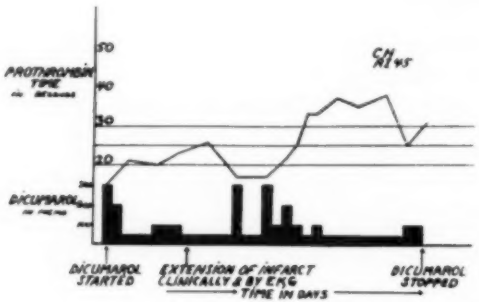


CHART IV. Illustrating inadequate dosage early with a resulting extension of the infarct; later adequate therapeutic levels were attained.

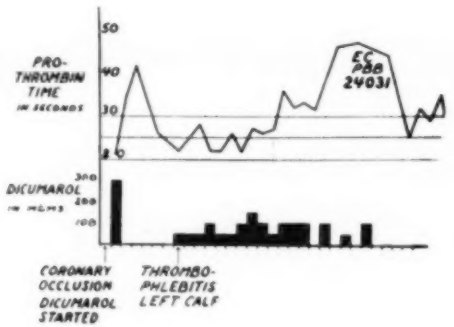


CHART V. A therapeutic level was attained but held for only three days. Three days after the return to subminimal levels thrombophlebitis developed.

anticoagulant therapy. There has been little change in the ratios between the control group and the patients receiving anticoagulant treatment either for deaths or thrombo-embolic phenomena from the statistics on 300 cases upward. The results to date indicate that the incidence of deaths from coronary thrombosis can be reduced from approximately 23 per cent to 13 per cent, or between one-third and one-half, and the incidence of thrombo-embolic complications can be reduced from approximately 19 per cent to 9 per cent, or one-half by the proper use of anticoagulant therapy. This means in reality that by the intelligent use of this new approach one person in three who would be expected to die from a specific attack of coronary occlusion will survive that attack, and that one-half of the anticipated thrombo-embolic complications can be prevented. No attempt can be made at this time to evaluate the effect of this on the factors of longevity and activity of the surviving patients.

Therapeutic Failures. The problems of the failures have been the subject of intensive studies by Drs. Marple and Beck of the central laboratory. Charts 3, 4 and 5 illustrate certain factors in this regard. There is a minimal therapeutic level below which anticoagulants fail to achieve satisfactory results. The majority of so-called failures occur because this level is not reached and maintained. For dicumarol therapy this is indicated by the minimal prothrombin time of 30 seconds using a control time of 13 to 15 seconds.* For heparin therapy, the clotting time should be approximately three times the normal. It is not sufficient, therefore, to state that a patient has received anticoagulant therapy. The key questions which must be answered are: How much? How long? What levels of effectiveness were

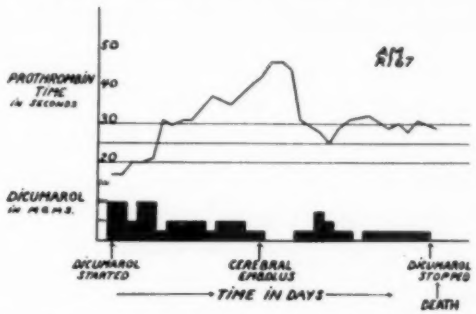


CHART VI. A true failure of dicumarol despite adequate administration.

obtained? How consistently were these maintained? With this information one can determine whether a failure was the responsibility of the drug or of those administering it. Although the majority of the failures brought to our attention have been due to inadequate dosage, a very small number of

* This equals 30 per cent maximum in our laboratory. In other words the therapeutic level is between two and three times the normal time.

patients continue to have thrombo-embolic episodes despite apparently adequate dosage of either heparin or dicumarol (chart 6). Some of these have malignancies of the liver, pancreas or elsewhere, others suffer from phlebitis migrans [13] and in some the cause has never been found.

TABLE V

Hemorrhagic Manifestations

	Total %	Severe %	Moderate %	Mild %	Unknown %
No anticoagulants (322)	3.7	0	0	2.8	0.9
Anticoagulants (409)	11.0	0.2	5.6	5.6	1.0
Anticoagulant only known cause	2.5				
Aggravation of basic cause	1.5				

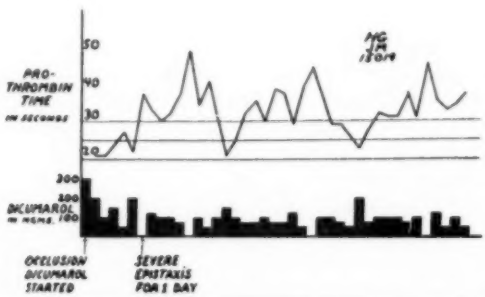


CHART VII. Illustration that all hemorrhages are not directly related to anticoagulant therapy and that if properly evaluated they *may* not be a contraindication to its use.

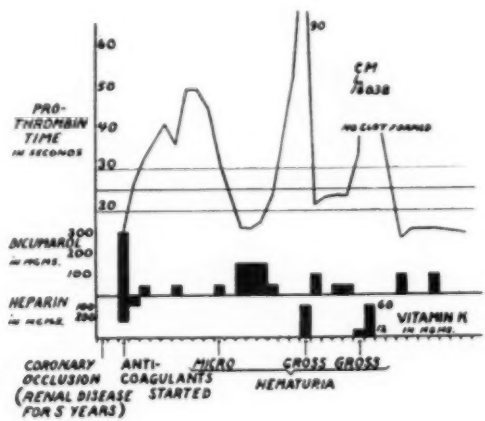


CHART VIII. Demonstrates the difficulties one may encounter in the use of anticoagulants in the presence of renal disease.

Hemorrhagic Complications. The occurrence of hemorrhage has also been studied in detail (table 5 and charts 7 and 8). It should be realized that although the incidence of hemorrhagic manifestations is somewhat higher in patients treated with anticoagulants, hemorrhages also occur in patients who have never received anticoagulants (in about 4 per cent of our cases). Serious hemorrhages are rare even among those treated with anticoagulants and are usually due to one of the following factors:

1. Poor prothrombin tests by the laboratory.
2. Lack of sufficiently careful thought and supervision by the physician, resulting in overdosage.
3. The use of anticoagulants in the face of known contraindications.

e.g.: (*a*) Blood dyscrasias
(*b*) Serious liver disease
(*c*) Serious renal disease especially with hematuria or calculi.
(*d*) Gastrointestinal ulceration or colitis.
(*e*) Others.

4. Unrecognized contra-indications such as those above listed, or

(*a*) Unknown peptic ulcer
(*b*) Unknown diverticulitis.

5. Recent surgery or injury—not sufficiently healed.

Animal studies by Blumgart et al.[14] and by Beattie et al.[15] have demonstrated that following ligation of a coronary artery the myocardial infarction area contains no more hemorrhage in dicumarolized animals than in non-dicumarolized animals. This confirms our original observations in man.[9]

The details of the completed study of this new approach to the treatment of coronary thrombosis with myocardial infarction will be presented at later meetings this year and will be published.

Rheumatic Heart Disease with Auricular Fibrillation and Multiple Embolization

The next patients to stimulate our interest were those who were suffering with old rheumatic heart disease, with auricular fibrillation, and who then developed intra-cardiac thrombi, from which multiple emboli were repeatedly cast off. These have previously represented among the most discouraging problems in medicine since neither the patient nor the doctor could predict when an embolus would cause the loss of an extremity, paralysis, or death. The former treatment has been largely fatalistic, accompanied by attempts to keep the heart in a state of compensation but with no assurance that this would prevent embolization.

The treatment of these cases was begun in the late summer of 1946, and reports of our results have been published.[13, 5, 16] To date 22 such patients have been treated first in the hospital and later on a permanent ambulatory

basis. As reported, patients who have had as many as 12 and even 20 emboli have ceased having emboli and in the six treated more than one year (one 19 months) no emboli have occurred. Difficulty in arranging to keep patients on long term ambulant anticoagulant therapy has produced problems and emboli have occurred in several individuals who have not been faithful to the regime, but it is apparent that ambulant long term dicumarol therapy is a distinct advance in the treatment of this extremely serious condition—though it is not an infallible one and it is a difficult regime for the patient and the doctor to follow indefinitely.

Long Term Ambulatory Anticoagulant Therapy

Experience with anticoagulants, especially dicumarol, in long term ambulatory treatment has been studied by Nichol and Fassett,[17] and by Foley and the author.[13] Certain of Nichol's cases have now been on dicumarol therapy for three and four years. We are reporting one series of 19 patients who have been on continuous dicumarol therapy for an average of nine months—the longest, for 18 months. The conditions for which such an approach seems advisable at present include:

1. Rheumatic heart disease with fibrillation and multiple embolic episodes.
2. Phlebitis migrans—persistent.
3. Recurrent thrombophlebitis including familial thrombo-embolic disease.
4. Recurrent coronary thrombosis with myocardial infarction.

This technic is fraught with inherent difficulties centering about the need for frequent (once or twice weekly) accurate prothrombin tests, close medical supervision, and intelligent coöperation on the part of the patient. The problems encountered and how they have been met are discussed in detail in the papers above referred to.

It has been demonstrated by laboratory tests and autopsy findings that prolonged treatment with dicumarol in clinical dosage does not result in damage to the kidneys or to the liver.

The Combined Use of Anticoagulants and Quinidine

Recently, interest has been refocused on the possibility of reducing the risk of embolization following the administration of quinidine for the restoration of normal rhythm in patients with auricular fibrillation. Saland [18] and his co-workers and others have had a considerable experience in this field. We have used it to some degree. There are numerous questions which arise regarding this controversial subject. Chief among these are: Is there an advantage in the conversion of a fibrillating heart to normal rhythm? Which cases should be selected for this approach? Will such a heart maintain regular rhythm sufficiently long to warrant any risk of conversion attempts? Does the use of quinidine actually increase the risk of emboliza-

tion? These questions have been the subject of numerous but not completely conclusive studies in the past. No attempt will be made to analyze them here or to evaluate the rôle of anticoagulants in this regard. The question is at present reopened for further investigation.

A Review of the Past and the Challenge of the Future

It now appears that the story of the use of anticoagulants in thromboembolic diseases will be a long and rewarding one. Only the first chapters have been written. These include:

1. The identification and production of heparin and dicumarol.
2. The demonstration that they inhibit clotting processes in vitro and in animals.
3. The establishment of their practical application and therapeutic usefulness in man.

Despite their great value in establishing the importance of this type of therapeutic approach, it is well known that neither heparin nor dicumarol is a completely satisfactory anticoagulant. The advantages and disadvantages of each have been adequately stressed in the literature and will not be repeated here.

It is essential for the full development of this form of therapy that future chapters include the production of new, improved anticoagulants and simpler methods for the control of their administration.

The following requirements should be fulfilled by the ideal anticoagulant:

1. It should be therapeutically active when administered orally or parenterally—without producing digestive or hypersensitivity reactions.
2. Its action should be rapid, affecting the clotting tendencies of the blood within one hour.
3. The dosage should be easily standardized and fairly uniform for a given patient and as between different patients. The action should be predictable in terms of quantitative response.
4. It should be relatively non-toxic with a wide safety zone between therapeutic effect and toxic damage to important organs. It is obvious that there will always be some hazard from bleeding essential to the very nature of this therapeutic approach. This should not be regarded as a toxic effect but rather as an overextension of the therapeutic effect of the drug.
5. The action of the drug should be promptly terminated after stopping its administration or following the use of an effective antagonistic agent which in itself is free from undesirable effects.
6. A test for the activity of this substance should be sufficiently simple to permit its control by the family physician or, even better, by the patient.
7. The anticoagulant should be inexpensive.

The development of such a drug would greatly broaden the application of anticoagulant therapy. The fact that an extremely high percentage of persons in the older age groups die or are crippled by thrombotic episodes raises interesting questions regarding the widespread prophylactic use of such a drug, as first suggested by E. V. Allen.

Summary and Conclusions

1. The value of the anticoagulants dicumarol and heparin in the treatment of thrombophlebitis has been conclusively established.

2. The importance of the use of anticoagulants post-operatively in the prophylaxis of thrombo-embolic complications has been clearly demonstrated.

3. Data based on extensive studies indicate that the death rate from coronary thrombosis with myocardial infarction can be reduced one-third and the incidence of thrombo-embolic complications can be reduced one-half by the use of anticoagulants.

4. The majority of therapeutic failures to date have been the result of inadequate anticoagulant treatment. Some failures occur in spite of apparently adequate therapy.

5. Hemorrhagic complications occur in patients who have never received anticoagulants but are more frequent in those who have. These problems have been discussed.

6. The value of anticoagulants in the prophylaxis and treatment of the thrombo-embolic complications of auricular fibrillation appears significant.

7. The indications for long term ambulatory treatment with anticoagulants have been presented.

8. The question of conversion of auricular fibrillation to normal rhythm with quinidine, and the possible value of anticoagulants in this technic has been briefly presented.

9. The needs for and the requirements which should be fulfilled by an ideal anticoagulant have been outlined.

BIBLIOGRAPHY

1. Zilliacus, H.: On the specific treatment of thrombosis and pulmonary embolism with anticoagulants with particular reference to the post-thrombolic sequelae, 1946, Mecators Tryckeri, Helsingfors.
2. Allen, E. V., Hines, E. A., Kvale, W. F., and Barker, N. W.: The use of dicumarol as an anticoagulant: experience in 2,307 cases, Ann. Int. Med., 1947, xxvii, 371.
3. Barker, N. W., Hines, E. A., Kvale, W. F., and Allen, E. V.: Dicumarol, Am. Jr. Med., 1947, iii, 634.
4. Wright, I. S.: Practical considerations in the conservative treatment of thrombophlebitis, N. Y. State Jr. Med., 1946, xlvi, 1819.
5. Wright, I. S., and Foley, W. A.: Use of anticoagulants in the treatment of heart disease, Am. Jr. Med., 1947, iii, 718.
6. Allen, A. W., and Donaldson, G.: Personal communication, April 1948.
7. Brambel, C. E.: The use of anticoagulants in the prevention of thrombo-embolic complications. (Presented before the Sectional Meeting, American College of Surgeons, April 1947.)

8. WRIGHT, I. S.: Experiences with dicumarol in the treatment of coronary thrombosis, Proc. Am. Fed. Clin. Res., 1945, ii.
9. WRIGHT, I. S.: Experiences with dicumarol in the treatment of coronary thrombosis with myocardial infarction, Am. Heart Jr., 1946, xxxii, 20.
10. WRIGHT, I. S.: Experiences with dicumarol in the treatment of coronary thrombosis with myocardial infarction, Trans. Assoc. Am. Phys., 1946, lix, 47.
11. NICHOL, E. S., and PAGE, S. W. JR.: Dicumarol therapy in acute coronary thrombosis, results in fifty attacks, Jr. Florida Med. Assoc., 1946, xxxii, 365.
12. PETERS, H. R., GUYTHER, J. R., and BRAMBEL, C. E.: Dicumarol in acute coronary thrombosis, Jr. Am. Med. Assoc., 1946, cxxx, 398.
13. FOLEY, W. T., and WRIGHT, I. S.: Long term anticoagulant therapy for cardiovascular diseases. (Prepared for publication.)
14. BLUMGART, H. L., FREEDBERG, A. S., ZOLL, P. M., LEWIS, H. D., and WESSLER, S.: The effect of dicumarol on the heart in experimental acute coronary occlusion, Trans. Assoc. Am. Phys., 1947, lx, 227.
15. BEATTIE, E. J., CUTLER, E. C., FAUTEUX, M., KINNEY, T. D., and LEVINE, H. D.: The use of dicumarol in experimental coronary occlusion, Am. Heart Jr., 1948, xxxv, 94.
16. WRIGHT, I. S.: The use of anticoagulants in the treatment of diseases of the heart and and blood vessels, Bull. Philadelphia Coll. Phys., April 1947.
17. NICHOL, E. S., and FASSETT, D. W.: An attempt to forestall acute coronary thrombosis, South. Med. Jr., 1947, xl, 69.
18. SALAND, G.: Personal communication, April 1948.

CERTAIN CLINICAL ASPECTS OF THE APPLICATION OF WATER BALANCE PRINCIPLES TO HEART AND KIDNEY DISEASE *

By F. R. Schemm, M.D., F.A.C.P., *Great Falls, Montana*

During the past 15 years, my colleagues and I have been applying true water balance principles, with a proper regard for sodium and acid-base balance, to all our seriously ill patients. We have done this in all departments, surgery, obstetrics, pediatrics and medicine, for the prevention or correction of oliguria or anuria and azotemia, and of dehydration and edema. We have found this practice to be of value in the prevention of serious renal complications in general. We believe that, particularly in cardiovascular-renal disease where such complications are so frequently encountered, it has reduced our morbidity and mortality.

At the annual meeting of this college, six years ago, we stressed the observations we had made on patients with cardiac disease and edema.[1] This was done because of the common practice of restricting fluids in the presence of edema, especially in patients with heart disease. As Sir Francis Milman [2] put it, "lest futile and exploded theories be set against facts and experience," we cited some 400 observations which have grown to number over 1000. We saw, as he did in 1786, that "to irritate the body with medicines and prohibit drink is prejudicial to the patient and that treatment will be much more fortunate with large and frequent draughts of diluting drinks."

In our 1942 report we said that "a daily intake of 2500 to 3000 c.c. was adequate for the majority of cases." However, we did also confirm what Austin Flint [3] had said, "that *more than enough* water is *not too much*." For, in order to establish the point that it was safe to give whatever amounts of plain water might be dictated by water balance principles in the more seriously ill, "we often carried our intakes *higher than optimum* and repeatedly observed the rapid clearing of massive edema in the face of intakes averaging 6000, 7000, or 8000 c.c. daily."

In this paper we shall stress the water requirements in *renal disease* and in the renal complications of cardiac disease. For while renal function disturbances greatly increase the requirements of the body for water, there appears at this time to be such preoccupation with the protein and sodium requirements in renal disease that the water requirements are often ignored or disastrously underestimated.[4, 15, 16]

This may be because, as the President of the Medical College of Paris [5] suggested in 1721 in commenting on its virtues, "water is too common, too

* Presented before the meeting of the American College of Physicians, San Francisco, April 20, 1948.

From the Department of Medicine of the Great Falls Clinic, Great Falls, Montana.

much known, and, therefore, too little esteemed." More probably it is due to failure to appreciate the full significance of the work on renal function and insensible water loss done by Newburgh [6, 7, 8] about 20 years ago on the basis of which he was able to give quantitative expression to the water needs of the body. Coller [9, 10, 11] realized the significance of the work and extended it so effectively to the reduction of surgical morbidity and mortality that death in a brine-logged condition or from so-called postoperative nephritis is now more of a reproach than an alibi to a surgeon.

It is obvious that man's need for water is secondary only to his need for oxygen. Yet, in health, he maintains water equilibrium with an intake of only about one quart of water as such, plus one quart of water derived from his solid food, which is balanced by the loss by evaporation of about a quart of water from the lungs and skin for temperature regulation and about a quart of water eliminated as urine water to carry off the solids which demand excretion.* One of the most common manifestations of disease is the breakdown of this economical use of water.

In the past, we thought that three liters of water were more than enough for a sick person and that his development of anuria or edema was due to the inability of the kidneys to excrete water or salts. Studies in the last two decades, particularly of water metabolism and renal function, however, show that:

(1) Even badly impaired kidneys *can* excrete all the plain water that reaches them and can excrete the sodium and metabolic solids which reach them if enough water reaches the kidneys to provide them with from 2000 to 3000 c.c. of urine-water daily.

(2) The vaporization of water for temperature regulation in disease may demand as much as 2000 to 5000 c.c. of water before any can reach the kidneys.

(3) A preëxisting true dehydration, or plain water deficit, which is often encountered in the presence of edema as well as in its absence, may require for its correction from 4000 to 7000 c.c. of water before any reaches the kidneys.

(4) Retention of sodium salts, along with an excess of basic ash sufficient to neutralize the metabolic acids, results in the diversion of water to edema formation in amounts that might otherwise be adequate for the needs of the body.

(5) Extra acid sodium salts and nitrogenous wastes, in the presence of an insufficient supply of water, are eliminated in urine water derived from the expendable fraction (4000 to 7000 c.c.) of the 50 liters of body water, almost three-quarters of this water coming from the cells. The resultant cell dehydration seems to be more harmful to the cells of the body than either edema or azotemia.

* For simplification, the 200 c.c. ± of water of stool is considered to be balanced by preformed water or water of oxidation.

These facts show, to cite a quite ordinary example, that a patient, with a true dehydration from a previously inadequate intake, and with a fever, and a low fixed specific gravity, might require a total of 4000 c.c. for body water deficit replacement in the first day or two, and in addition might require 2000 c.c. daily for vapor loss, before any water could reach the kidneys. The kidneys themselves would then require 2000 c.c. daily of urine water to carry away the daily solids. Such a patient could be restored to normal balance only by giving 6000 c.c. daily for two days and 4000 c.c. daily thereafter, and not then unless unnecessary amounts of sodium or protein were avoided to prevent a diversion of water from the kidneys or an increase in total urinary solids. An intake of 3000 c.c. daily for this patient would merely increase his plain water deficit each day; and dehydration, anuria and azotemia could neither be prevented nor corrected.

Young people with normal kidneys who are deprived of only 4.5 liters of plain body water develop severe oliguria, a moderate retention of urea and salts, and evidence of renal injury in the form of albuminuria, casts and red cells.[9] The plain water deficit in the very ill often amounts to from 4.5 to 7 liters. Such a deficit results in a degree of cellular dehydration and of extracellular fluid concentration (true dehydration) [12] which is capable of injuring *normal* kidneys or of making *diseased kidneys* worse, or of precipitating a so-called "renal shut-down." The resistant anuria which results and is occasionally irreversible, is usually attributed entirely to the *inability* of the kidneys to excrete water or salt.[4] Actually, it appears that short of ligation of the ureters and the virtual suspension of cell function in truly terminal stages of disease, anuria and edema result in the vast majority of instances from exhaustion of body water and from the diversion of water (and salt) from the kidneys, and not from inability of the kidneys to excrete water and salt. Our observations show that this concept holds up well in practice. It can be applied by the estimation of water and sodium needs from relatively simple data, and by the satisfaction of these needs with the clinical and therapeutic technics described in our 1942 report.[1]

Other facts from these studies and from clinical experience should be emphasized:

(1) Not less than the estimated amounts of water should be given; if possible by mouth, but if necessary *without hesitation* by vein.[13, 14] The water of 1000 c.c. of an isotonic solution of dextrose in distilled water is swiftly diffused throughout all 50 liters of the body water; while a similar volume of isotonic sodium chloride is distributed rapidly but throughout only 14 liters of extracellular fluid; blood and plasma volumes are added to about 6 liters of circulating blood.

(2) With rehydration and a large volume of urine water, mercurial diuretics can be used safely in nephritis and often with great benefit, whereas with an inadequate water supply they may induce evidence of renal injury in patients with originally normal kidneys. In the most resistant cases

however, a good output of urine water, with an adequate restriction of sodium and the use of mercurials, may be ineffective in clearing edema until enough acid is supplied to augment the action of the metabolic acids and "mobilize" sodium.

(3) Serious loss of salt, plus water, may occur in the course of treatment of edema with acid and mercurial diuretics and extremely low sodium diets, as well as from vomiting, diarrhea or profuse diaphoresis. But *brine* is not *water*, and the replacement of body fluid loss and the correction of acute disturbances of electrolyte pattern with *saline* solutions should be accompanied by the simultaneous maintenance of a true water balance with *plain water*.

(4) In acute deficits of sodium or protein small amounts of either will promptly correct the deficit. But in advanced chronic disease, the low carbon dioxide combining power and low serum proteins are only transiently affected or affected not at all, by large amounts of sodium or protein, which may harmfully divert water from the kidneys and increase the amount of solids (nitrogenous wastes and sodium salts) to be excreted by the kidneys.

Many cases of advanced nephritis are relatively asymptomatic and quite active with a carbon dioxide combining power of around 20 volumes per cent, a level which appears to be dictated by the functional state of the kidney rather than by lack or loss of sodium. In these cases small amounts of acid drugs do not disturb the sodium level and can be safely used, only, however, with an adequate amount of urine water.

The level of the serum proteins in chronic nephrotic syndromes is similarly determined by the level of impairment of the synthesis and exchange of protein and not by lack or loss of protein. Edema which has resisted high protein diets and as much as 75 grams of sodium-free human albumin daily can be cleared with the ingestion of only 40 grams of protein daily and the proper manipulation of water and sodium. If synthesis and exchange are improved, the serum proteins are even seen to rise on this 40 gram protein intake.

We have outlined a few of the facts and experiences which explain our therapy.[1] These have led us, for example, to avoid the use of sodium salts with sulfonamides for they often divert so much water from the kidneys that, in spite of an alkaline urine, oliguria and crystallization develop, while the latter do not develop when a large volume of dilute *acid* urine is maintained. The crystallization of sulfonamides in the tubules and anuria can be corrected without recourse to decapsulation of the kidneys: thus, one of our patients received 16 liters of water in 36 hours to break successfully an absolute anuria that had persisted for 42 hours.

Data in reports on cases submitted to decapsulation of the kidneys and, more recently, on those submitted to peritoneal or intestinal lavage suggest that the development of what are considered the indications for these procedures might have been prevented or the results of lavage improved, had the same pains been taken to maintain true and adequate water balance as

were taken in maintaining sodium and protein balance.[15, 16, 17] Thus in one such report,[18] a patient with renal injury and moderate fever showed a progressing oliguria and azotemia which culminated in complete anuria by the eighth day, when he was submitted to peritoneal lavage. The data show that in the eight days before operation he received what were considered to be proper amounts of R-molar lactate and protein which yielded coincidentally a total of 56 grams, or 7 grams daily, of sodium salts, while in these eight days he had received only 1800 c.c. of water daily. This amount of water could not correct any antecedent water deficit and was scarcely enough to provide for the demands of vaporization alone. The development of complete anuria was, therefore, inevitable. The greatest recorded intake of water in the other case reports was an average of 3000 c.c. daily.[17]

The following briefly outlined cases from our series illustrate our observations and practice in patients with obliguria or anuria, and azotemia and edema in cardiac or renal disease: *

Cases given an adequate amount of water to correct a severe preëxisting dehydration commonly follow the pattern illustrated by R. W. S. during the time in which their water deficit is being made up.

This patient was admitted five days after an acute myocardial infarction with edema and Adams-Stokes convulsions. Urine, heavy with albumin, was obtained by catheter six hours after admission in the amount of 125 c.c., to end an anuria of 20 hours' duration. In the first 24 hours almost all of the 5000 c.c. of water received was taken up by thirsty cells or vaporized so that only 775 c.c. of water reached the kidneys to form urine. There was the usual slight increase in edema, but with this, as is often seen, there was a marked general improvement as evidenced by clearing of the sensorium and, in this case, the cessation of convulsions, well before diuresis began. In the next 14 hours, 4100 c.c. of urine water were elaborated (intake 3500 c.c.), and the blood urea dropped from 75 to 23 mg. and the edema began to clear.

An example of the free use of intravenous solutions in a patient with severe injury of the myocardium and so-called renal shut-down is presented in the patient. E. P. He was admitted five days after a posterior infarction with a blood urea of 196 mg. An anuria of 42 hours' duration was overcome only after 10 liters of water had been received; the urine obtained was bloody. His average daily intake of 5000 c.c., which was largely dissipated by fever and diaphoresis, was attained with from 2000 to 3000 c.c. daily of isotonic dextrose by vein. In spite of this intake, his relative oliguria and his edema persisted until the fourteenth day, when following a drop in his temperature, which lessened his vaporization demands, diuresis began and the clearing of edema and azotemia was rapid.

Our practice in the replacement of salt and water loss (loss of extracellular fluid, commonly referred to as dehydration) is illustrated by A. V. F.

* Much fuller data on some of these cases and many others are presented in Part II of the 1942 report.[1]

who was seen in extreme shock with marked hypochloremia and oliguria following a period of vomiting and diarrhea. In five days she tolerated 30 liters of water with 80 grams of salt, the equivalent of 9 liters of isotonic sodium chloride plus 21 liters of plain water, a ratio of 1 to 2, which is about the lowest ratio of brine to water that we use. The 20 liters of plain water provided for vaporization loss and an adequate amount of urine water, and did not hinder correction of the hypochloremia and restoration of volume of the extracellular fluid. She responded rapidly and edema was not produced although she was fibrillating, had both mitral stenosis and aortic insufficiency, and had been edematous four days before admission.

An example of our management of cases with chronic glomerulonephritis with nephrotic features and cardiopathy, and with low serum proteins with a low serum albumin is seen in F. G. In an earlier hospital admission elsewhere it had been felt necessary to restrict fluids, give a high protein diet, and augment the osmotic pressure of the blood with acacia in order to clear his edema. A year later, we were able to clear his edema in eight days on an average daily intake of 5000 c.c. with a "neutral" diet yielding only 40 grams of protein. The serum protein and serum albumin remained at about 4 and 2 grams per cent respectively; later a diet protein of 120 grams did not increase these levels. As his disease progressed a carbon dioxide combining power of 20 to 30 volumes per cent permitted moderate activity, and extra sodium as R-molar lactate only produced thirst and edema without producing more than a slight transient effect on the carbon dioxide combining power level.

Our practice in acute fulminating hemorrhagic nephritis with scanty, bloody urine or anuria is indicated by M. S. who was admitted in coma after two convulsions. All of her intake, for the first six and one-half days before her coma was relieved, was by vein and averaged 4000 c.c. daily. The sodium received in 1500 c.c. of blood and plasma about equalled that lost in approximately 3000 c.c. of emesis and stool. In spite of 9500 c.c. of water in the first 56 hours the oliguria became worse until only a few c.c. of bloody urine per hour were being elaborated. In the next 28 hours, however, when attention was directed to the mobilization of sodium by acidification and 10.5 grams of ammonium chloride were given along with 5000 c.c. of water by vein the renal shut-down was overcome and 4000 c.c. of urine were elaborated. For the next eight days an average output of urine of 2500 c.c. daily was maintained and there was steady clinical improvement, in spite of a drop in the carbon dioxide combining power from 52 to 33 volumes per cent and without either clearing of edema or actual diuresis. In the next seven days edema cleared, while the carbon dioxide combining power rose, on a low sodium, 40 gram protein diet. She was maintained on this diet until there was no evidence of residual nephritis and renal function tests were normal.

Comment

Although Newburgh summarized his studies on *The Importance of Dealing Quantitatively with Water in the Study of Disease* in 1933, there is evidence in the current literature [4, 15, 16, 17] of a lag in the application of these principles to problems in internal medicine. This is disturbing, for it is well known that what Sir James MacKenzie called a "true scent" in medicine may be lost and buried for generations.

As long ago as 1706, a Fellow of the Royal College of Physicians [5] was on such a "true scent." He speaks of insensible perspiration and regards retained salts as responsible for thirst. He finds that the urine from a sick man contained "but the thirtieth part of those salts usually found in a sound man's urine so that, of necessity, salts must remain behind and be left like so many French Dragoons to quarter on the blood and fluids at discretion." He remarks that "These salts creep with the chyle into the blood and have no way out but by the urine, and that for dissolving these salts, that water is best which has least content." Here, buried for over 200 years, is awareness on a qualitative basis of the effect of an undue accumulation of salts in the body, and of the need of the body for plain water for vaporization purposes, for the uses of the kidneys, and for the correction of true dehydration.

The importance of these requirements of the body for water in serious illness should not be lost sight of in our preoccupation with the requirements of the body for protein and sodium, which, although very important, do not lessen and often themselves increase the need of the body for plain water.

Conclusion

In applying water balance principles in renal disease and in the renal complications of cardiac disease for the correction or prevention of anuria, azotemia and edema we have found it especially important to keep in mind:

1. That the increase in the plain-water needs of the body in serious illness is often of great magnitude.
2. That water does not reach the kidneys until all the other demands of the body for water have been satisfied, and
3. That brine is not water. The sodium laden water of Ringer's, R-molar lactate and Tyrode's solutions, and of ordinary plasma and of blood, as well as the water of isotonic sodium chloride solutions, should not be counted in the plain-water intake, because their water cannot be satisfactorily used for the metabolic purposes of plain-water.

BIBLIOGRAPHY

1. Schemm, F. R.: A high fluid intake in the management of edema, especially cardiac edema. I. The details and basis of the regime, Ann. Int. Med. 1942, xvii, 952–969. II. Clinical observations and data, Ann. Int. Med., 1944, xxi, 937–976.
2. Milman, Sir Francis: Animadversions on the nature and cure of the dropsy, 1786, J. Walker, London, p. 122.

3. FLINT, AUSTIN: A treatise on the principles and practice of medicine, (6th ed.), 1886, Lea Bros.
4. THORNE, G. W., and TYLER, F. H.: Clinical management of edema in Bright's disease, Med. Clin. N. Am., 1947 (Sept.), 1077–1090.
5. FLOYER, SIR JOHN and BAYNARD, E.: History of cold bathing, both ancient and modern, 4th. ed., Vol. 2, Wb. Innys, London.
6. NEWBURGH, L. H., JOHNSTON, M. W., and FALCON-LESSES, M.: Measurements of total water exchange, Jr. Clin. Invest., 1930, viii, 161–196.
7. NEWBURGH, L. H., and LASHMET, F. H.: A comparative study of the excretion of water and solids in normal and abnormal kidneys, Jr. Clin. Invest., 1932, xi, 1003–1009.
8. NEWBURGH, L. H., and LASHMET, F. H.: The importance of dealing quantitatively with water in the study of disease, Am. Jr. Med. Sci., 1933, clxxxvi, 461–470.
9. COLLER, F. A., and MADDOCK, W. G.: A study of dehydration in humans, Ann. Surg., 1935, cii, 947–960.
10. MADDOCK, W. G., and COLLER, F. A.: Water balance in surgery, Jr. Am. Med. Assoc., 1937, cviii, 1–6.
11. COLLER, F. A., CAMPBELL, K. N., VAUGHAN, H. H., JOB, L. V., and MOYER, C. A.: Post-operative salt intolerance, Ann. Surg., 1944, xix, 533.
12. NADAL, S. W., PEDERSEN, S., and MADDOCK, W. G.: Two contrasting types of dehydration, Univ. Hosp. Bull. Ann Arbor, 1941, vii, 53–55.
13. WARTHEN, H. J.: Massive intravenous injections, Arch. Surg., 1935, xxx, 199–227.
14. CUTTING, R. A.: Cause of death resulting from massive infusions of isotonic solutions, Arch. Surg., 1939, xxxviii, 599–616.
15. BASSETT, S. H., et al.: Nitrogen and fluid balance in treatment of acute uremia by peritoneal lavage, Arch. Int. Med., 1947, lxxx, 616–636.
16. ODEL, H. M., and FERRIS, D. O.: Continuous lavage of the small intestine as a means of treating renal insufficiency, Proc. Staff Meet. Mayo Clin., 1948, xxiii, 201.
17. DAUGHERTY, G. W., ODELL, H. M., and FERRIS, D. O.: Continuous lavage of the colon as a means of treating renal insufficiency, Proc. Staff Meet. Mayo Clin., 1948, xxiii, 209.
18. GILSON, J. S.: Personal communication, unpublished data, 1947.

CLINICAL OBSERVATIONS WITH FAGARINE*

By D. Scherf, F.A.C.P., A. M. Silver and L. D. Weinberg,
New York, N. Y.

Although there has been considerable progress in therapy recently, new remedies for the treatment of cardiac arrhythmias deserve attention. Anyone who has seen a patient die as the result of persistently rapid heart rate in a paroxysmal tachycardia, refractory to digitalis, quinidine, and other drugs even in large doses, will welcome a new therapeutic agent.

Alpha-fagarine hydrochloride,† an alkaloid extracted from the Argentinean plant *Fagara coco*, has been recommended for certain disturbances of stimulus formation.[1] It has been used in man,[10, 11] and available reports suggested that further studies of the drug were justified.

Method

During the clinical use of fagarine in a small series of cases, arrhythmias in form of multifocal ventricular extrasystoles were observed [10]; we decided, therefore, to use this drug mainly in hopelessly ill patients suffering from advanced cerebral arteriosclerosis, metastatic carcinoma, uremia, etc. Many of the patients were over 70 years old. Not only did they present a cardiac lesion, usually in the form of coronary sclerosis with auricular fibrillation, but their systemic condition and debility could not help but influence their cardiac status.

Fagarine was injected intramuscularly in an amount of less than 2 mg. per kilogram when the weight could be determined. The weight of the patient was estimated when conditions precluded actual weighing.

Lead II of the electrocardiogram was obtained before the injection and every five to 15 minutes following the injection for two hours or longer. Whenever observation of the string showed a change in cardiac activity, the electrocardiogram was immediately registered.

The blood pressure was also determined every 10 or 15 minutes and the patient was constantly observed for appearance of untoward signs.

Results

Case 1. P. M., an 86 year old white female, had suddenly become paralyzed and lost the power of speech. There had been a cerebrovascular accident 36 years previously with some residual aphasia and right hemiparesis. According to the information obtained from the family physician, auricular fibrillation had been continuous for a long time with moderate hypertension. On admission, the blood pressure was

* Received for publication March 20, 1948.
Aided by a Grant from Bernhard Altmann.
From the Department of Medicine, the New York Medical College, New York, N. Y.
† We are grateful to the Laboratorias Apotarg in Cordoba, Argentine, for the supply of alpha-fagarine hydrochloride used in our study.

160/100 mm. Hg. The heart was enlarged to the left and auricular fibrillation was present. A systolic aortic murmur was audible. There was a right hemiplegia. Little change was noted in her condition on a regime of physiotherapy and digitalis in the amount of 0.1 gram per day.

Digitalis was discontinued one week before fagarine was given. The dose of the latter amounted to 0.06 gram by intramuscular injection. The blood pressure over a two hour period showed a gradual decline from 150/90 to 134/74 mm. Hg with essentially no change in the condition of the patient. The electrocardiogram showed no change, but next morning normal sinus rhythm was found for the first time.

Two days later, the patient had sudden lower left chest pain; she became cold and clammy and developed pulmonary edema. She died on the fourth day after the injection. Another electrocardiogram taken just prior to death revealed the persistence of the sinus rhythm.

Postmortem examination revealed coronary sclerosis, myocardial degenerative changes, old posterior wall infarction, aortic atheromatosis, and left lower lobe bronchopneumonia. The cause of death was ascribed to a new posterior wall infarction.

Summary: An 86 year old woman with repeated cerebral accidents, hypertension and auricular fibrillation received an injection of 0.06 gram of fagarine. This was not followed by any change in the electrocardiogram or in the condition of the patient during an observation period of two hours. Sinus rhythm supervened, however, within the next 12 hours and persisted until death.

Case 2. A. M., an 87 year old white male, was admitted for an attack of syncope. He was disoriented and presented a picture of dehydration, malnutrition, and cerebral arteriosclerosis. There had been a sudden onset of loss of speech one year previously without paralysis followed by some improvement. The heart was slightly enlarged and showed a rapid, irregular ventricular rate. The electrocardiogram on admission showed auricular flutter with varying 2:1 and 4:1 block. During the administration of digitalis, the flutter temporarily stopped but recurred and persisted.

On the twenty-second day in the hospital, 0.06 gram of fagarine was injected intramuscularly but the electrocardiogram taken at the time of the injection showed that the patient had spontaneously developed normal sinus rhythm. There was neither subjective nor objective evidence of a disturbance ascribable to the fagarine. No significant changes of the blood pressure were observed.

Figure 1 shows the form of the RS–T segment and the T-waves before, and 30, 50 and 90 minutes after the injection. There was a very slight depression of the RS–T segments and no change in the form of the T-waves. The P–R interval measured 0.24 second before and after the injection and throughout the period of observation.

Summary: The injection of 0.06 gram of fagarine in an 87 year old patient was followed by no untoward symptoms. The electrocardiogram showed only slight changes. Sinus rhythm was present at the time of the injection.

Case 3. R. M., a 65 year old woman, was admitted with a history of chills and fever for one day. A number of years previously she had been told that her blood pressure was high and she knew that diabetes mellitus existed three months prior to this admission; auricular fibrillation had also been discovered at another hospital.

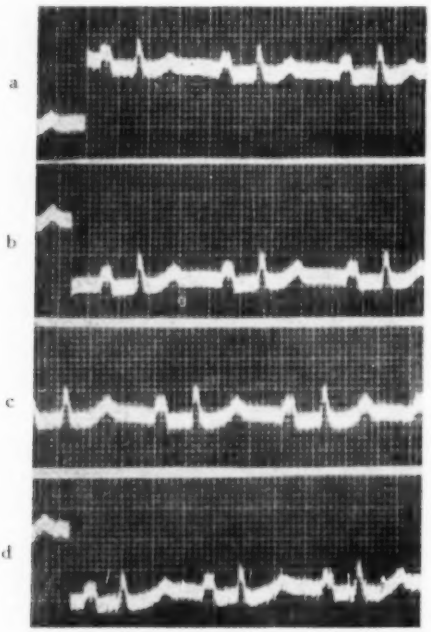


FIG. 1. The top tracing shows Lead II before the injection of 0.06 gram of fagarine; the other tracings represent Lead II taken at intervals of 30, 50 and 90 minutes respectively after the injection (case 2).

On admission, the patient was confused, uncoöperative, dyspneic and cyanotic. There was evidence of left lower lobe pneumonia with a temperature of 40° C. The heart was enlarged to the left and the pulse was irregular with a ventricular rate of 128. There was an apical systolic murmur. The blood pressure was 120/60 mm. Hg. The pneumonia resolved during two weeks of penicillin therapy and the diabetes was controlled with 20 units of protamin-zinc insulin. The cardiac rate continued to be irregular but went down to 100 without administration of digitalis.

The patient received 0.09 gram of fagarine intramuscularly. Fifteen minutes later she complained of buzzing in the ears. This diminished after 30 minutes and disappeared after two hours. During the observation period of two hours and 15 minutes, the blood pressure varied from 132/70 to 150/90 mm. Hg.

The electrocardiogram showed auricular fibrillation with left axis deviation before the injection. There was no change during the observation period of two hours after the injection. The auricular fibrillation persisted and the QRS complexes as well as the T-waves showed no variation.

Summary: In a 65 year old woman with auricular fibrillation, diabetes and pneumonia, the injection of 0.09 gram of fagarine produced no electrocardiographic effect.

Case 4. C. G., a 68 year old white male, was admitted with the history of a right hemiplegia which occurred on the previous day. Hypertension had existed for at least five years; the patient had suffered from a right hemiplegia four years prior to admission with complete recovery. Physical examination revealed Cheyne-Stokes respiration, a flaccid paralysis of the right side and motor aphasia. The cardiac rate was very rapid and totally irregular because of auricular fibrillation. Apical and aortic systolic murmurs were present. The blood pressure was 240/128 mm. Hg.

The electrocardiogram (figure 2) showed auricular fibrillation with rapid ventricular rate. There was marked left axis deviation with a left ventricular strain pattern; the QRS complexes were plump and slurred but only 0.10 second wide. The RS–T segments were depressed in Lead I and showed a convexity directed upward. They were followed by deeply inverted T-waves. The opposite direction of QRS segments and T-waves was also visible in Lead III. The chest leads indicated left ventricular hypertrophy.

Before any digitalis was administered, 0.12 gram of fagarine was injected into the gluteal muscles. The blood pressure at that time was 230/100 mm. Hg. New determinations were made at 10 minute intervals for one hour, and at 15 minute intervals for the second hour. The variations did not exceed 20 mm. Hg in the systolic pressure or 20 mm. upward in the diastolic pressure. There were no untoward symptoms after the injection.

Five minutes after the injection, there were no changes in the electrocardiogram but 10 minutes after the injection the auricular fibrillation changed into auricular flutter and a series of ventricular extrasystoles originating in one focus occurred (figure 3a). Fifteen minutes after the injection (figure 3b), the auricular flutter had disappeared and sinus rhythm with marked disturbances of stimulus formation in the sinus node was present. The P-waves were variform. The length of the P–R interval varied and premature blocked P-waves were visible. Ventricular extrasystoles still persisted. This picture remained without change although the disturbances were even more pronounced 70 minutes after injection (figure 3c). Gradually, the number of normal sinus impulses increased and extrasystoles diminished. Three hours after the injection, regular sinus rhythm was registered (figure 3d). Sinus rhythm persisted and was present when the patient was discharged 10 days later.

Summary: In a 68 year old man with hypertension, old and recent hemiplegia, and auricular fibrillation, 0.12 gram fagarine caused auricular flutter within 10 minutes. Sinus rhythm appeared in 15 minutes with marked disturbances of stimulus formation and conduction. There were no other untoward effects.

Case 5. M. Y., a 45 year old white female, was admitted because of cold sweats, insomnia, palpitation, and nervousness of five days' duration. For 22 years she had had recurrent episodes with similar complaints, of sudden onset and sudden termination with increasing frequency lasting from a few days to a few hours. On admission, she was moderately dyspneic, pale, with slight cyanosis of the lips. The heart rate was 160 and the rhythm was regular. The heart sounds were of equal intensity (embryocardia).

Paroxysmal tachycardia of supraventricular origin (figure 4a) with a rate of 200 was found in the electrocardiogram and the patient was given 0.1 gram of fagarine. There were no symptoms referable to the injection nor were there any changes in the many electrocardiograms taken over a two hour period (figure 4b). The blood pressure varied between 110/86 and 90/70 mm. Hg. Two days later, after administration of a total of 1.0 milligram of digitoxin in dosage of 0.25 mg. every two hours, a normal sinus rhythm was registered (figure 4c).

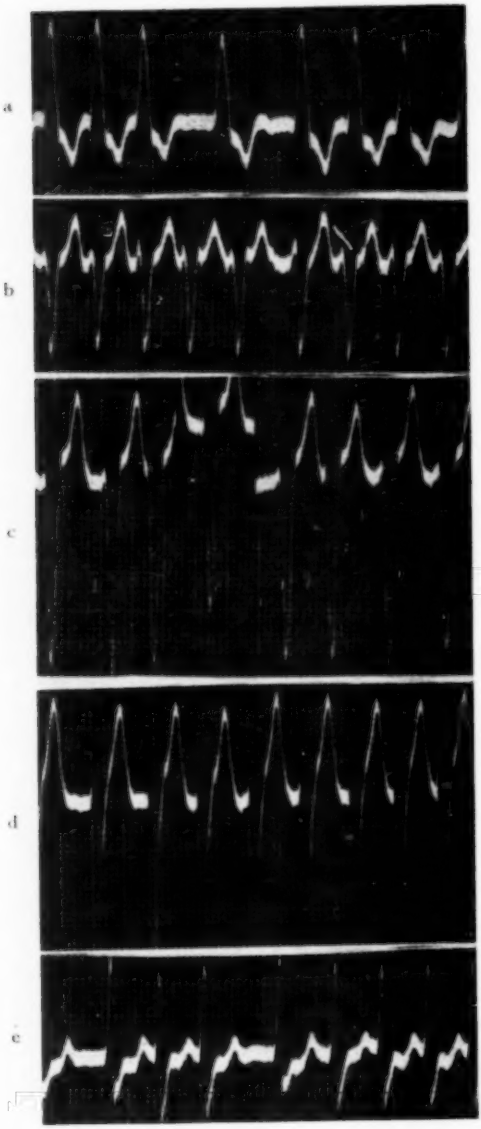


FIG. 2. Three standard leads, leads CF_R and CF_5 of case 4 before the injection, showing auricular fibrillation and changes compatible with left ventricular hypertrophy.

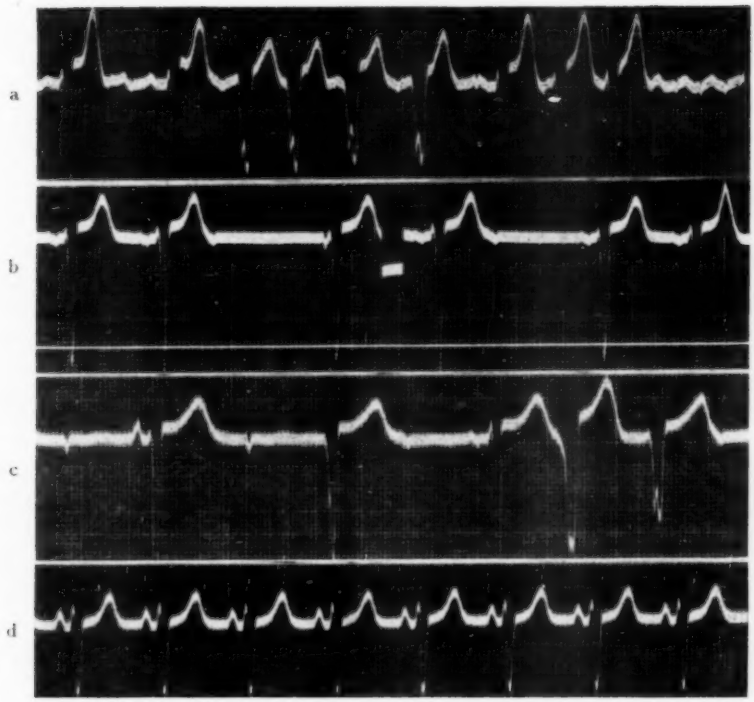


FIG. 3. Figure 3a shows auricular flutter and multiple ventricular extrasystoles 10 minutes after the injection; figure 3b, 3c and 3d were obtained 15, 70 and 180 minutes after the injection respectively (case 4).

Summary: 0.1 gram of fagarine was given to a 45 year old woman with paroxysmal supraventricular tachycardia. There was no effect in the electrocardiographic picture of the tachycardia and there were no untoward symptoms from the injection.

Case 6. L. C., a 64 year old Chinese male, was admitted in a semi-stuporous condition with left hemiplegia associated with ipsilateral sensory impairment. The heart was enlarged to the left and apical and aortic systolic murmurs were present. The blood pressure was 220/130 mm. Hg on admission and fell to 180/110 subsequently. The patient improved with physiotherapy but was unable to walk or care for himself. Auricular fibrillation with low, slurred, though not widened QRS complexes was noted in the electrocardiogram.

Fagarine in the amount of 0.06 gram was injected. During the following observation period of two hours, there was no change in the blood pressure and no symptoms appeared referable to the injection. The drug was repeated one week later in dose of 0.08 gram, again without appreciable change. The same electrocardiogram with the exception of ventricular extrasystoles originating in one focus was

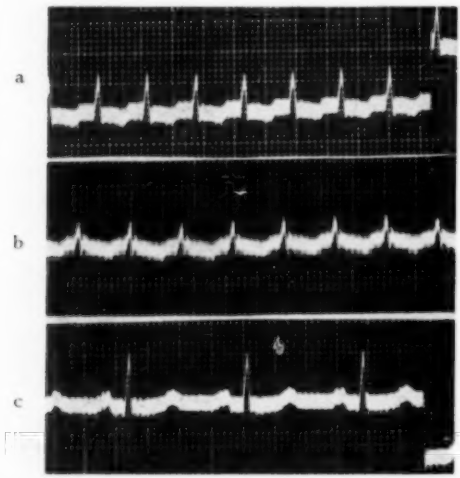


FIG. 4. Figure 4a shows Lead II of a paroxysmal auricular tachycardia recorded before the injection of fagarine; 4b represents Lead II after the injection. Figure 4c shows sinus rhythm two days later, after digitalis administration.

obtained in the two and one-half hour observation period after the injection. The fibrillation persisted.

Summary: The injection of 0.06 and again of 0.08 gram of fagarine in a 64 year old man with hypertension and hemiplegia produced no effect.

Case 7. A. L., an 88 year old female, was admitted for general weakness and exertional dyspnea. These signs had persisted for a year and had on previous occasions been somewhat relieved by digitalis.

Examination revealed a heart of normal size and shape and a blood pressure of 100/80 mm. Hg. Cheyne-Stokes respiration was present. There was marked dextroscoliosis with emphysema. The liver was slightly enlarged. Blood chemical findings were a nonprotein nitrogen of 135, urea N of 65 and creatinine of 3.2 mg. per cent.

The electrocardiogram showed auricular flutter with a 4:1 block, left axis deviation, and marked slurring of the QRS complexes (figure 5a). After digitalization there was no diminution of the evidence of congestive failure nor of the azotemia. The auricular flutter pattern persisted and therefore fagarine was injected intragluteally in the amount of 0.06 gram.

The blood pressure rose in the following 50 minutes from 108/50 to 136/60 mm. Hg and gradually fell again at the end of 100 minutes to 108/50 mm. Hg; 25 minutes after the injection, the respirations became more forceful and somewhat irregular, but no untoward symptoms appeared.

Ventricular extrasystoles had been present occasionally before the injection (figure 5a), but they increased in number 26 minutes after the injection and were apparently multifocal. Forty-five minutes after the injection, auricular fibrillation appeared (figure 5b) and changed quickly into normal sinus rhythm (figure 5b). Multiform ventricular extrasystoles appeared (figure 5c).

The patient improved markedly, the evidence of cardiac failure diminished, the blood chemistry became normal, and the patient was finally discharged from the hospital with normal sinus rhythm.

Summary: In an 88 year old woman with auricular flutter, the administration of 0.06 gram of fagarine caused transition to auricular fibrillation and sinus rhythm within 45 minutes. Multifocal ventricular extrasystoles appeared as a transient phenomenon in the otherwise uneventful transition.

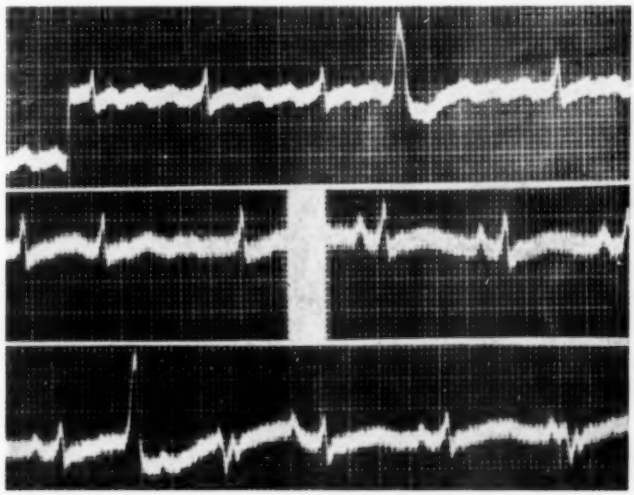


FIG. 5. Auricular flutter and a ventricular extrasystole before the injections are shown in figure 5a (case 7). The first part of figure 5b shows auricular fibrillation, the second part sinus rhythm 45 minutes after the injection. Later multiform ventricular extrasystoles appeared (figure 5c).

Case 8. M. O'B., a 94 year old white male, was admitted to the hospital in a disoriented state. The history was unobtainable until later when the patient said he had suddenly lost consciousness for an indeterminate period prior to admission. Examination showed distant heart sounds and a blood pressure at 130/80 mm. Hg. There was auricular fibrillation. The patient was obviously undernourished and improved rapidly on a high caloric, high vitamin diet without digitalis. Cardiac findings persisted unchanged.

The patient, who weighed 150 pounds, received 0.06 gram of fagarine. Ten minutes after the injection, he complained of slight dizziness and headache; the latter disappeared after 20 minutes, the former after an hour. The blood pressure rose to 140/80 mm. Hg in the first 30 minutes following the injection and fell in the succeeding 60 minutes to 128/68 mm. Hg.

The electrocardiogram prior to the injection showed auricular fibrillation with some slurring of the QRS complexes but no other notable changes (figure 6a). Ten minutes after the injection, multiform ventricular extrasystoles appeared. These increased in number and in frequency (figure 6b) 20 minutes after the injection. The heart showed regular sinus rhythm 35 minutes after the injection (figure 6c).

Two months later sinus rhythm was still present.

Summary: Sinus rhythm appeared within 35 minutes after the injection of 0.06 gram of fagarine to a 94 year old man with auricular fibrillation. Multifocal ventricular extrasystoles, headache, and vertigo followed the injection.

Case 9. D. P., a 79 year old male, was admitted in a semistuporous state, confused and disoriented. No history was obtainable. The patient was dyspneic, orthopneic and cyanotic. There were râles over both bases, more marked over the left. The ventricular rate equalled the pulse rate at 160 per minute, but the rhythm occasionally seemed somewhat irregular. The heart sounds were muffled and percussion was unsatisfactory because of emphysema. The blood pressure was 172/80 mm. Hg. The liver was enlarged and there was marked edema of the legs. A hard, irregular sessile mass was palpated rectally and thought to be a carcinoma. The condition of the patient remained very poor; two injections of cedilanide (0.4 mg. each), administered intravenously in 24 hours, were without influence on the tachycardia.

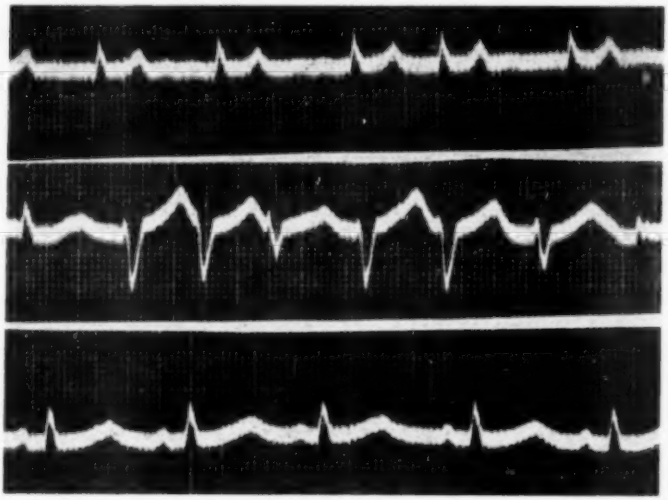


FIG. 6. Figure 6a shows auricular fibrillation before the injection (case 8). Multiform ventricular extrasystoles are present 20 minutes after the injection (figure 6b), and sinus rhythm appears 15 minutes later (figure 6c).

Fagarine (0.12 gram) was given intramuscularly four days later. The blood pressure fell to 120/70 mm. Hg within 40 minutes, then slowly rose to 158/68. Simultaneously with the fall of blood pressure, a bradycardia appeared.

The electrocardiogram taken before injection of fagarine showed a regular tachycardia with a rate of 133. During the short diastoles, P-waves unrelated to the QRS complexes were occasionally visible (figure 7a). A ventricular tachycardia originating above the bifurcation of the bundle (A–V-nodal or stem tachycardia) with independent activity of the auricle was diagnosed. Six and one-half minutes after the injection the ventricular rate was 93 and the ventricular complexes showed changes which were apparently caused by the slower rate only. Again, the auricles contracted

independently of the ventricles (figure 7b). Twenty-six minutes after the injection the electrocardiogram shown in figure 7c was obtained. Suddenly abnormal ventricular complexes appeared, apparently due to an aberrant ventricular conduction. Some of the ventricular complexes in this tracing were similar to those in figures 7a and 7b, but were wider by 0.02 second and the T-waves were lower. Sixty minutes

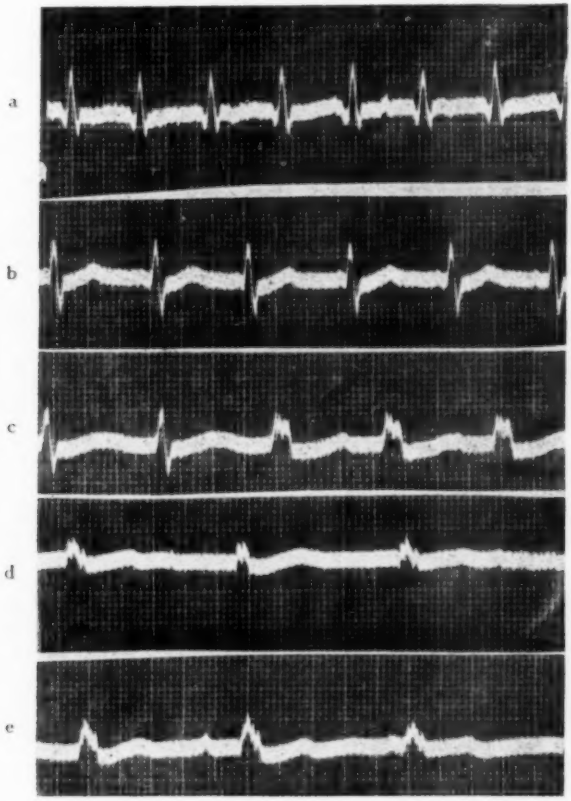


FIG. 7. Figure 7a shows a heterotopic ventricular tachycardia; slowing of the heart and independent action of auricles and ventricles appeared six and one half minutes after the injection (figure 7b). Figure 7c, figure 7d and figure 7e were obtained 26, 60 and 85 minutes after fagarine.

after the injection (figure 7d) the ventricular complexes were lower but otherwise similar to those in figure 7c. The ventricular rate was 58. The auricles contracted irregularly and independently of the ventricles. A similar tracing is visible in figure 7d obtained 85 minutes after the injection. The next morning the electrocardiogram showed the same picture as figure 7a.

The condition of the patient progressively deteriorated and he died on the seventh day of hospitalization.

FIG. 8. Change from auricular fibrillation to sinus rhythm 10 minutes after the injection (case 10).

Summary: The injection of 0.12 gram of fagarine in a 79 year old man with systolic hypertension and cardiac failure, presumably the result of coronary sclerosis, and a heterotopic tachycardia, caused only a temporary slowing of the rate and an intraventricular block.

Case 10. A. P., a 57 year old woman, was admitted with a history of cardiac disease of many years' duration, but the precise nature of the condition was unknown. The present illness began three days before admission with a cough productive of blood streaked sputum. She experienced palpitation of the heart and had been given 0.2 mg. of digitaline Nativelle daily for two days before admission. A slowly increasing mass in the neck had been noted over a 10 year period; this was associated with increased nervousness, tremor and perspiration. On physical examination, both lobes of the thyroid were enlarged. The heart appeared to be of normal size and the sounds were loud and clear. There was marked hypermotility of the heart. The blood pressure was 140/78 mm. Hg. The heart rate was 128 per minute and auricular fibrillation was present. Râles were present in both bases. The temperature was 39° C. With penicillin the temperature became normal in a few days. She weighed 145 pounds.

An intramuscular injection of 0.1 gram of fagarine was given three days after the last dose of digitalis. Ten minutes after the injection, the pulse became regular. There was no change in the blood pressure and no untoward symptoms followed the injection.

Figure 8 shows the change from the auricular fibrillation to regular sinus rhythm, interrupted occasionally by single or small groups of auricular extrasystoles. Later these disappeared completely. No other changes were demonstrable in the electrocardiogram.

Two days later the auricular fibrillation recurred and persisted continuously. The patient signed her release from the hospital 18 days later.

Summary: A 57 year old woman with hyperthyroidism and auricular fibrillation developed sinus rhythm 10 minutes after the injection of 0.1 gram of fagarine. No untoward symptoms were observed.

Case 11. M. R., a 70 year old man, was admitted in a semicomatose condition following an accident. Besides a fractured left hip the patient had a very fast pulse with a rate of 136 per minute. Under the mistaken impression that a paroxysmal tachycardia was present, he was given 0.08 gram of fagarine. There was no response clinically and no changes were found in the electrocardiogram; no complications ensued from the injection.

The electrocardiogram taken before fagarine was given (figure 9a) showed a sinus tachycardia with a rate of 136. The

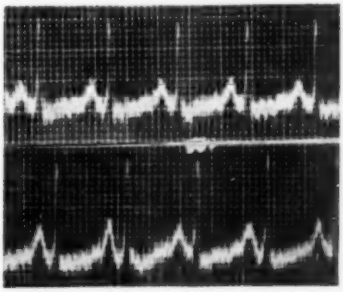


FIG. 9. Sinus tachycardia before (figure 9a) and after (figure 9b) the injection of fagarine (case 11).

same tachycardia with the same rate and the same ventricular complexes was recorded 60 minutes after the injection (figure 9b).

The patient died five days later as a result of his injuries.

Summary: A 70 year old patient admitted with sinus tachycardia received 0.08 gram of fagarine without any change in the electrocardiographic picture.

Case 12. S. B., an 83 year old male, was admitted with complaints of abdominal distention and absence of bowel movements for one week. On admission the patient was drowsy and displayed muscular twitchings. The pulse was irregular with a rate of 82 per minute, the respiratory rate was 21 per minute. The heart was slightly enlarged to the left and soft mitral and aortic systolic murmurs were heard. The blood pressure on admission was 142/82 mm. Hg. The abdomen was distended and tympanitic. A right indirect irreducible hernia was present. Azotemia was present with a non-protein nitrogen of 120, an urea nitrogen of 71 and creatinine of 3.1 mg. per cent. The electrocardiogram showed auricular flutter with 4:1 block and widened QRS complexes (figure 10a).

Fagarine in the amount of 0.12 gram was injected intramuscularly. The blood pressure was 212/125 mm. Hg. Five minutes after the injection the patient had a seizure of tonic and clonic convulsions with pupils directed upward and with no response to stimuli. He was pulseless and no blood pressure could be obtained. Respirations were about 5 per minute, slow and deep. In two minutes the seizure disappeared and the blood pressure was 210/110 mm. Hg. The pulse was slightly irregular and respirations were normal. The electrocardiogram obtained during the seizure shows that a ventricular tachycardia had appeared with a rate of 230 and with varying forms of the ventricular complexes (figure 10b). Ten minutes after the injection the blood pressure was again 210/120 mm. Hg and the patient appeared the same as before the seizure. Auricular flutter was still present (figure 10c) but the auricular rate had diminished from 330 (figure 10a) to 300. Twenty minutes after the injection there was a second convulsive episode similar to the first which again lasted for two minutes. The electrocardiogram taken during this seizure showed the same picture as figure 10b. A few minutes later the blood pressure rose to 240/120 and the patient again recovered. Thirty minutes after the injection the blood pressure was 180/110 mm. Hg with a full, strong, slightly irregular pulse. The electrocardiogram taken at this time (figure 10d) showed sinus rhythm with occasional

ventricular extrasystoles and a rate of 80 per minute. Forty minutes after the injection the pulse was regular and full but three minutes later another convulsion developed and lasted for five minutes. An electrocardiogram taken during this seizure showed a ventricular tachycardia (ventricular flutter?) with a rate of 230

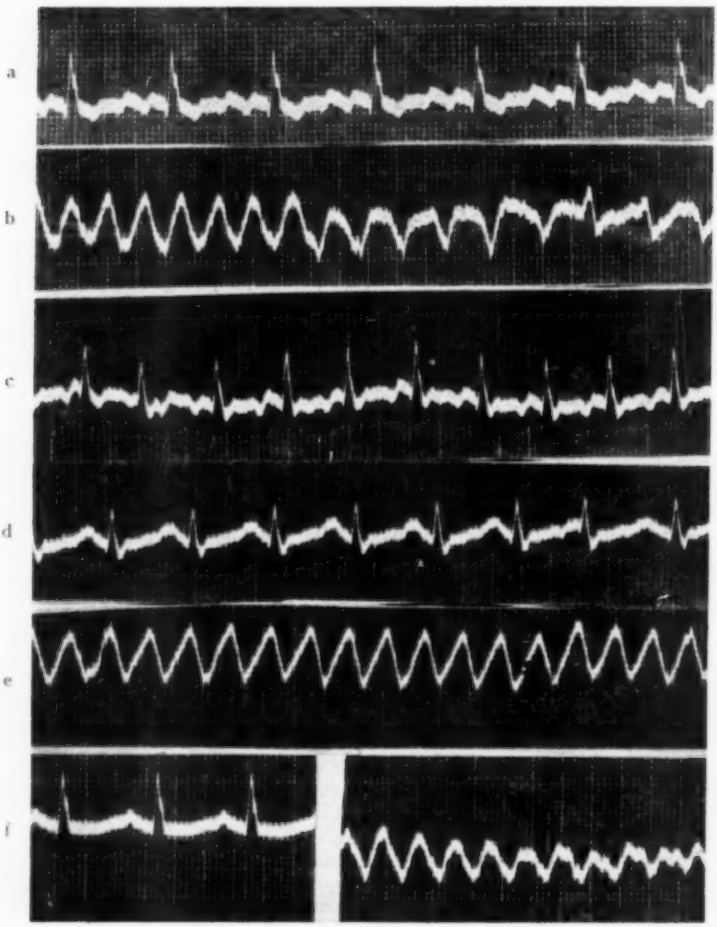


FIG. 10. Figure 10a shows auricular flutter before the injection (case 12). Figure 10b shows ventricular tachycardia during an attack of Stokes-Adams syndrome 5 minutes after the injection. Auricular flutter with slower auricular rate and 2:1 block was registered 10 minutes after the injection (figure 10c), and sinus rhythm was present 20 minutes later (figure 10d). Ventricular flutter appeared 43 minutes after the injection (figure 10e). Sinus rhythm followed by ventricular fibrillation was registered 2 hours after the injection (figure 10f).

(figure 10e). Atropine in the amount of 0.5 mg. was injected intravenously without any noticeable effect. In the following 30 minutes the blood pressure was well maintained and the patient appeared comparatively well. Sinus rhythm was present with a rate of 85 (first part of figure 10f). One hour and 40 minutes after the injection of fagarine the pressure had dropped to 130/70. Exactly two hours after the injection, the patient had his fourth convulsive episode during which he succumbed. The electrocardiogram showed that ventricular fibrillation had appeared with this final episode (figure 10f).

Summary: Administration of 0.12 gram of fagarine to an 83 year old man with intestinal obstruction, azotemia, and auricular flutter was followed by sinus rhythm, but an attack of ventricular tachycardia and ventricular fibrillation appeared and led to sudden death.

Case 13. S. S., a 72 year old white female whose weight was 150 pounds, was admitted with a history of swelling of the ankles and fullness of the abdomen. These complaints, with breathlessness, had recurred repeatedly for two years.

On admission the patient was dyspneic and disoriented. The heart sounds were loud and pure; there was a rapid heart rate and an irregular rhythm. The blood pressure was 130/90 mm. Hg. The hypermotility of the heart associated with a tremor and exophthalmus suggested hyperthyroidism. Propylthiouracil was administered in the amount of 150 mg. daily and digitalization was started with 0.1 gram of digitalis leaf twice daily.

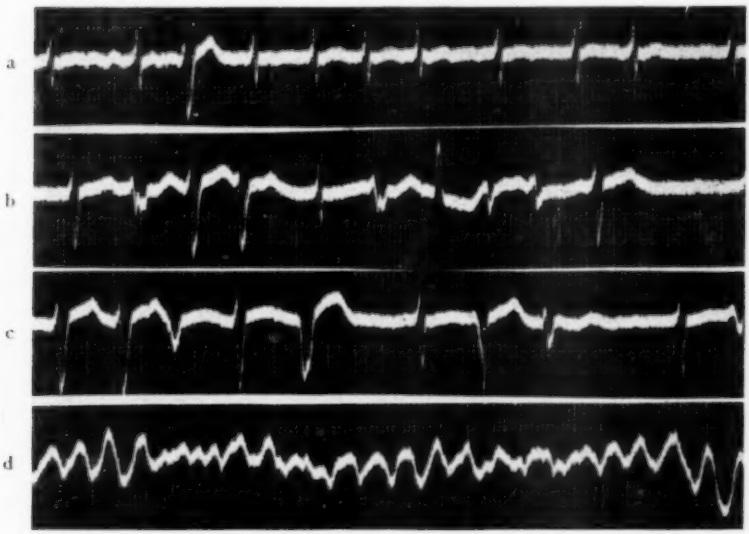


FIG. 11. Figure 11a shows auricular fibrillation and a ventricular extrasystole before the injection (case 13). Multiform ventricular extrasystoles appeared 17 minutes (figure 11b) and 33 minutes after the injection (figure 11c). Ventricular fibrillation appeared 60 minutes after the injection (figure 11d).

The digitalis was discontinued after a trial and 14 days after discontinuation, 0.05 gram of fagarine was injected intramuscularly. There was a drop of 20 mm. Hg of the systolic and the diastolic blood pressures, but otherwise the patient appeared unchanged. However, one hour after the injection the patient suddenly collapsed and soon ceased to breathe.

Figure 11a was obtained before the injection of fagarine and shows auricular fibrillation with a single ventricular extrasystole. Seventeen and 33 minutes after the injection, there was an increasing number of variform ventricular extrasystoles (figures 11b and 11c). The electrocardiographic picture remained unchanged until 60 minutes after the injection when ventricular fibrillation appeared (figure 11d). At no time was sinus rhythm observed.

Summary: In a 72 year old woman with hyperthyroidism and auricular fibrillation, the administration of 0.05 gram of fagarine led to multifocal ventricular extrasystoles and ventricular fibrillation.

Discussion

The cardiac depressant action of an alkaloid extracted from *Fagara coco* was observed by Stuckert and Sartori in 1932.[9] Fagarine, an alkaloid identical with alpha-fagarina hydrochloride used by us, was later studied experimentally.[4, 5] It was found to raise the threshold of the heart to fibrillation caused by faradization and to diminish the risk of ventricular fibrillation following ligation of coronary arteries. During the wartime scarcity of quinine, Deulofeu and co-workers called attention to fagarine as a remedy for certain tachycardias and fibrillation. In dogs and rabbits it was found that doses of 0.005 gram per kilogram could be given intravenously three times daily for 45 days without incurring immediate or subsequent disturbances.[11] Tacquini gave 0.06 to 0.1 gram of fagarine intramuscularly to six patients with auricular fibrillation. Sinus rhythm appeared in all cases within 40 minutes.[1]

A clinical study of the effect of fagarine on human subjects was conducted.[10] The drug restored sinus rhythm in two cases with auricular flutter and in four of five patients with auricular fibrillation. Sinus rhythm appeared within 20 to 50 minutes after intramuscular administration of the drug. In the six cases where sinus rhythm was restored, the dose employed varied between 0.08 and 0.1 gram. In the patient in whom the drug was unsuccessful, the dose was 0.05 gram. Two of the patients experienced slight dizziness following the injection; one vomited and his electrocardiogram showed multiple ventricular extrasystoles and ventricular flutter. At the Inter-American Cardiologic Congress in Mexico City, Tacquini reported on his further clinical experiences with fagarine.[11] Untoward results were observed in some patients. He warned not to give the drug to digitalized patients. Doses of 0.08 to 0.1 gram were satisfactory. The drug was administered to 25 normal individuals in doses of 0.5, 0.6, 0.7, and 0.8 gram (0.01 gram/kg. body weight). Some patients had previously been completely digitalized, and no toxic symptoms were observed. The Q–T in-

terval was increased in all patients. Depression of the RS–T segment and diminution of the T-wave were seen. The electrocardiographic effects were reduced in most cases when 0.001 gram of atropine was given intravenously. Since doses as small as 0.005 gram per kilogram have a definite effect on cardiac muscle, the author advises starting with a considerably smaller dose which is far below the toxic level.

Data collected from our 13 cases are compiled in table 1. Fourteen injections were given to 13 patients whose ages varied between 45 and 94; eight patients were over 70 years of age. The dose employed was from 0.05 to 0.12 gram. All patients had some disturbance of the cardiac rhythm; in seven patients auricular fibrillation was present, and in three auricular flutter. Five of the patients had hemiplegia, and hyperthyroidism existed in two. The observations on all 13 patients are of interest with regard to their response to the drug. In evaluating the response of an abnormal rhythm to fagarine, two cases must be discarded. In one, the existing auricular flutter had disappeared just before the injection was given, and in the other only sinus tachycardia was present at that time.

In six of the 11 cases, the existing arrhythmia was abolished and sinus rhythm supervened. In one instance the arrhythmia, auricular fibrillation, was not arrested within the two-hour observation period after the injection, but it disappeared within the succeeding 10 hours. Similarly, the auricular fibrillation disappeared four hours after the injection in one case reported by Tacquini.[10] We feel justified in assuming that the fibrillation, which had persisted for many months before the injection, disappeared because of the administration of the drug.

It is difficult to evaluate the effect of fagarine in case 9. A heterotopic tachycardia probably originating in the ventricles above the bifurcation of the A–V conduction system existed. The stimuli formed there were not reversely conducted to the auricles so that the latter contracted independently from the ventricles. Following fagarine the tachycardia disappeared temporarily and a slow heterotopic ventricular rhythm appeared.

We consider this a successful use of fagarine. The return of the tachycardia after the fagarine effect wore off is to be expected in certain types of tachycardias (*extrasystolies à paroxysms tachycardiques*).[3, 7]

Our tenth case, similarly, demonstrated a return of auricular fibrillation within two days. This finding would be anticipated in many cases of hyperthyroidism.

Most regrettable were the accidents in the last two cases, where the injection was certainly the cause of the appearance of ventricular fibrillation.

In case 12 the first attack of Stokes-Adams syndrome caused by prefibrillary ventricular tachycardia or ventricular flutter, appeared only five minutes after the injection. In view of the rapidity of onset and of the existing azotemia, it seemed probable that the condition of the patient made his response to the injection abnormal. We decided, therefore, to continue the investigation. The next injection was given to a patient in good gen-

TABLE I

Case No.	Initials	Age	Sex	Clinical Diagnosis	Prevailing Rhythm	Fagarine Dose in Grams	Effect of Fagarine	Side Effects in ECG	Other Side Effects
1	P. M.	86	F	Hemiplegia, generalized arteriosclerosis	Auricular fibrillation	0.06	No immediate effect; sinus rhythm next morning	0	0
2	A. M.	87	M	Generalized arteriosclerosis	Sinus rhythm	0.06	0	0	0
3	R. M.	65	F	Diabetes mellitus, pneumonia, hemiplegia	Auricular fibrillation	0.09	No effect	0	Buzzing in the ears
4	C. G.	68	M	Hypertensive cardiovascular disease, hemiplegia	Auricular fibrillation	0.12	Sinus rhythm	Many ventricular extrasystoles, sinus arrhythmia, A-V block	0
5	M. Y.	45	F	Paroxysmal tachycardia	Paroxysmal supraventricular tachycardia	0.10	No effect	0	0
*6	L. C.	64	M	Hypertensive cardiovascular disease	Auricular fibrillation	0.06 0.08	No effect No effect	0 Ventricular extrasystoles	0
7	A. L.	88	F	Emphysema, generalized arteriosclerosis, azotemia	Auricular flutter	0.06	Sinus rhythm	Multifocal ventricular extrasystoles	0
8	M. O'B.	94	M	Generalized arteriosclerosis	Auricular fibrillation	0.06	Sinus rhythm	Ventricular extrasystoles	0
9	D. P.	79	M	Hypertensive cardiovascular disease	Heterotopic tachycardia	0.12	Bradycardia, intraventricular block	Multifocal ventricular extrasystoles	0
10	A. P.	57	F	Hyperthyroidism	Auricular fibrillation	0.10	Sinus rhythm	0	Headache, vertigo
11	M. R.	70	M	Hip fracture	Sinus tachycardia	0.08	No effect	0	0
12	S. B.	83	M	Hypertensive cardiovascular disease, hemiplegia, intestinal obstruction	Auricular flutter	0.12	Sinus rhythm followed by ventricular fibrillation	Ventricular flutter and fibrillation	Stokes-Adams attacks due to ventricular flutter and fibrillation
13	S. S.	72	F	Hyperthyroidism	Auricular fibrillation	0.05	Ventricular fibrillation	Multifocal ventricular extrasystoles	0

* Received two injections in successive weeks.

eral condition and the amount was only 0.05 gram. Unfortunately, the patient developed lethal ventricular fibrillation even before the auricular fibrillation disappeared. The hyperthyroidism itself, though it may have increased sensitivity to fagarine, was most probably not the only factor involved in the accident, because another patient with hyperthyroidism and of approximately the same body weight (case 10) tolerated 0.1 gram of fagarine very well. With this unfortunate and dramatic experience the investigation was immediately stopped. We are unable to decide whether the simultaneous administration of propylthiouracil was responsible for the regrettable accident.

Multifocal extrasystoles appearing in patients with coronary sclerosis, myocardial infarction, or following administration of digitalis or strophanthin are always an ominous sign. They occurred in five patients in addition to the one (case 13) who developed ventricular fibrillation. It is notable that in one observation (case 12), ventricular flutter and fibrillation supervened without the appearance of multifocal extrasystoles. Such extrasystoles are often seen following ligation of the coronary arteries in the experimental animal, but occasionally ventricular fibrillation starts without the preceding appearance of extrasystoles.

In case 6 the administration of 0.06 gram of fagarine caused no response while the injection of 0.08 gram, a few days later, was followed by the appearance of ventricular extrasystoles. Multifocal ventricular extrasystoles were also seen by Tacquini in one observation.[10]

In case 12, not only was there extremely rapid disappearance of auricular fibrillation, but an early onset of ventricular fibrillation with death. In view of the appearance of ventricular fibrillation in two cases and a serious augmentation of ventricular extrasystoles in others, the risk engendered in the use of fagarine is great. It is to be stressed that four cases showed no response to the drug and in these cases, despite the administration of relatively large doses (up to 0.1 gram), there were no changes in the existing rhythm.

Except in the last two cases the untoward symptoms were trifling. Only headache, buzzing in the ears, and vertigo occasionally appeared. There were no complaints in eight patients. The electrocardiographic changes were also slight. We confirmed the observations of Tacquini who also saw prolongation of the Q–T interval, depression of the S–T segment and lowering of the T-waves. Because of the smaller doses employed in our studies, these changes were of lesser extent and frequency than in the observation of Tacquini.

Remarkable is the early appearance of the effects of the injection in some cases. In case 4 distinct changes were visible within 10 minutes and in case 10 the auricular fibrillation changed into sinus rhythm after the same time interval. Case 8 showed multifocal ventricular extrasystoles 10 minutes after the injection. In case 12 the first attack of ventricular flutter appeared only five minutes after the injection. Great care was always taken to avoid an intravenous injection.

It is of interest that in case 4 fagarine changed auricular fibrillation into auricular flutter before sinus rhythm was established, while in case 7 flutter gave way to fibrillation before sinus rhythm appeared.

Only in one patient were respiratory alterations in form of more forceful breathing observed (case 7). The abnormal respiration in case 12 was certainly the consequence of the disturbance of the activity of the ventricles.

The point has already been stressed that death occurred in one of our cases who received 0.12 gram, which was the largest dose employed by us, and in another patient of approximately the same weight after a dose of 0.05 gram. The dose of 0.12 gram had previously been administered to two other patients in both of whom multifocal ventricular extrasystoles appeared. The slightly smaller dose of 0.1 gram was tolerated well without complications. On the other hand, in one patient the dose of 0.05 gram was followed within 25 minutes by ventricular fibrillation. While most other patients were in very poor physical condition, case 13 was not very ill. Case 7 had ventricular extrasystoles before the administration of fagarine and developed multifocal extrasystoles afterward.

Following the intravenous injection of fagarine in dogs a temporary moderate rise of blood pressure was observed.[6] We found a similar rise in four cases (cases 3, 4, 7, 8). Occasionally a temporary fall was seen (case 1) or a moderate rise *and* fall, as in case 9.

It is, in general, rarely necessary to abolish auricular fibrillation; most of the cases are treated successfully with digitalis and rarely does their condition further improve if they are "defibrillated." If defibrillation seems necessary, one succeeds in most cases with oral administration of quinidine. The same holds for the paroxysmal tachycardias. Only rarely is one unsuccessful in abolishing a tachycardia through one of the vagal reflexes or with oral administration of quinidine. Too frequently the physician immediately tries one of the injectable preparations recommended for this purpose. Such injections must be given if the vagal reflexes are ineffective or if quinidine is not tolerated or does not produce results. We recently lost a 46 year old patient with a fresh myocardial infarction, who developed a paroxysmal ventricular tachycardia which did not respond to quinidine, even in the dose of 6.0 grams daily. For such cases an effective and non-toxic drug is highly desirable. In cases of auricular flutter occasionally digitalis and quinidine, even in large amounts do not bring about a change to fibrillation or sinus rhythm; therefore treatment with other drugs becomes desirable and necessary. Unfortunately, our experiences do not show fagarine to be the ideal drug for these indications. The search for such a substance should be continued and justifies, in our opinion, the investigation reported in this paper. Recently investigations [2] show that it might be possible to detain non-toxic and effective antifibrillatory agents, related to fagarine.

Previous digitalization is considered a contraindication to the use of fagarine by Tacquini and his colleagues.

The observation of depression of abnormal, heterotopic stimulus formation and simultaneous excitement of stimulus formation in other centers is observed with many other well known substances often used in cardiology. Thus digitalis may both suppress and excite abnormal stimulus formation in the form of extrasystoles and tachycardias. Potassium salts may also abolish or cause ventricular fibrillation and it seems clear that the mode of action does not depend on the dose alone. Even quinidine and quinine, which are the best known substances for abolishing arrhythmias, may cause extrasystoles [12] and, even in relatively small doses, cause ventricular fibrillation if given intravenously.[8] We therefore think that in spite of the unfortunate experiences in cases 12 and 13 the drug should not be discarded peremptorily and experimental studies with it should be continued. We feel particularly encouraged by its action in animal experiments where doses up to 0.004 gram/kg. given *intravenously* to dogs by one of us [6] were tolerated well and always immediately abolished auricular flutter or fibrillation; no extrasystoles or other disturbances of rhythm appeared. Furthermore, huge doses were given to patients with healthy hearts by Tacquini without untoward results.[11]

Summary

Fourteen intramuscular injections of alpha-fagarine hydrochloride were given to 13 patients, whose ages varied between 45 and 94. Eight patients were over 70 years old. The dose varied between 0.05 and 0.12 gram. In six patients the existing arrhythmia disappeared promptly after the injection. In two patients, however, fatal ventricular fibrillation appeared. In five other cases dangerous multifocal ventricular extrasystoles were observed.

The response of the 13 patients to the drug is discussed in detail. Fagarine cannot, as yet, be recommended for clinical use. Further experimental studies with this interesting drug may lead to the discovery of an active and non-toxic agent.

BIBLIOGRAPHY

1. Deulofeu, V., Labriola, R., Orias, O., Moisset de Espanes, E., and Tacquini, A.: Fagarine, a possible substitute for quinidine, Science, 1945, cii, 69.
2. DiPalma, J., and Lambert, J. J.: Importance of the methoxy group in antifibrillatory compounds, Science, 1948, cvii, 66.
3. Gallavardin, L.: Extra-systolie ventriculaire à paroxysmes tachycardiaques prolongés, Arch. d. mal. du coeur, 1922, xv, 15.
4. Moisset de Espanes, E.: Action de la fagarine I et de la quinidine sur la fibrillation ventriculaire primaire produite par l'occlusion coronarienne expérimentale, Compt. rend. Soc. de biol., 1938, cxxvii, 233.
5. Moisset de Espanes, E., and Moyano Navarro, B.: Action cardiaque et hemodynamique de la fagarine I, Compt. rend. Soc. de biol., 1938, cxxvii, 510.
6. Scherf, D.: The effect of fagarine on auricular fibrillation and flutter, Proc. Soc. Exper. Biol. and Med., 1948, xvii, 59.

7. Scherf, D., and Boyd, L. J.: Clinical electrocardiography, 2d ed., 1946, Lippincott, Philadelphia.
8. Schwartz, S. P., and Jezer, A.: The action of quinine and quinidine on patients with transient ventricular fibrillation, Am. Heart Jr., 1934, ix, 792.
9. Stuckert, G., and Sartori, A.: Rev. Univ. Nac Cardoba, Argentina, 1932, xix, 12.
10. Tacquini, A. C.: Tratamiento de la fibrilacion y del aleteo auriculares con clorhidrato de fagarina, Rev. argent. de cardiol., 1945, xii, 83.
11. Tacquini, A. C.: Fagarine—a new drug for the treatment of auricular fibrillation and flutter, Am. Heart Jr., 1947, xxxiii, 719.
12. Wilson, F. N., and Wishart, S. W.: Effects produced by the intravenous injection of quinidine and other drugs upon the mechanism of the heart beat, Trans. Assoc. Am. Phys., 1926, xli, 55.

XANTHOMATOUS BILIARY CIRRHOSIS (A CLINICAL SYNDROME) *

By H. Edward MacMahon and S. J. Thannhauser,
Boston, Massachusetts

Evidence of skin xanthoma with chronic jaundice and liver disease in relatively rare cases has been recognized for a long time and recorded in the literature by various authors: Addison and Gull,[1] 1851; Moxon,[2] 1873; Pye-Smith,[3] 1873; Hutchinson, Sangster and Crocker,[4] 1882; Balzer,[5] 1884; Hardaway,[6] 1890; Futcher,[7] 1905; Posner,[8] 1909; Chvostek,[9] 1911; Dyke,[10] 1928; Weidman and Freeman,[11] 1924; Buerger,[12] 1934; Weidman and Boston,[13] 1937. However, no attempts were made to match various characteristic symptoms to a definite clinical entity. Thannhauser and Magendantz [14] in 1937 and Thannhauser [15] in 1940 described as "xanthomatous biliary cirrhosis" a typical clinical syndrome characterized by the following features:

1. Skin xanthoma of the "plain and tuberous" variety.
2. Enlarged liver and spleen.
3. Obstructive type of jaundice of years' duration.
4. Extremely high values for total cholesterol (increased four to eight times those of normal) as well as for lecithin (increased four to eight times those of normal in serum).
5. The serum is transparent and not creamy despite the outstanding increase of cholesterols and lecithin. Low values for neutral fat in the serum are found.

Since the publication of Thannhauser and Magendantz's paper similar observations have appeared by Comfort, Shepard, and Snell,[16] Herbert,[17] Eusterman and Montgomery,[18] and Layani, Laudat and Astruc,[19] Hoffbauer, Evans and Watson,[20, 21] and Gebhardt.[22] Thannhauser and Magendantz in 1937 were not in a position to report autopsy findings of their cases.

Moxon and Fagge [23] as well as Pye-Smith (1873) reported autopsies of three cases showing xanthoma of the skin and atheromatous changes on the inner lining of the arteries as well as xanthoma formation on the lining of the bile ducts. Pye-Smith described the changes in the liver as revealing a slight degree of interstitial cirrhosis. "The patches in the ducts looked just like atheroma in the artery with which condition, indeed, they corresponded histologically."

Depending on these findings, Thannhauser and Magendantz suggested

* Received for publication October 25, 1947.
From the Joseph H. Pratt Diagnostic Hospital and Tufts College Medical School, Boston, Massachusetts. Aided in part by grants from the Rockefeller Foundation and the Godfrey Hyams Trust Fund.

that xanthoma formation of the larger bile ducts producing xanthomatous scar tissue may be the cause of the clinical syndrome described as xanthomatous biliary cirrhosis. It was their opinion that the development of the xanthoma of the skin as well as the xanthoma formation on the lining of the bile ducts was the expression of a systemic disease characterized by increased new formation of cholesterol and hypercholesteremia (hypercholesteremic xanthomatosis). The xanthomatous involvement of the large bile ducts and their partial obstruction was thought to be the primary event which resulted later in this special type of biliary cirrhosis.

In the meantime autopsies were performed on three cases of xanthomatous biliary cirrhosis, none of them showing xanthomatous changes of the lining of the bile ducts. It is the purpose of this paper to clarify the mechanism which may lead to the development of the well-defined clinical syndrome of xanthomatous biliary cirrhosis. The detailed clinical histories and laboratory findings of five cases observed over a long period, three autopsies, and four biopsies at our disposal taken at an early stage of the disease will provide the basis for this report.*

Clinical Cases with Autopsies and Biopsies

Case 1. D. L. M., a 44 year old French-Canadian woman, was admitted to the Joseph H. Pratt Diagnostic Hospital in November 1939. The patient stated that she had been perfectly well until 1937 when she first noticed icterus of her sclerae and skin. Although at that time she had no abdominal pain, she became severely nauseated and vomited every morning. She developed anorexia and lost about 30 pounds within four months. She also observed severe pruritus of the skin, especially of her arms. She had no fever or chills. Her stools were clay-colored. Her urine was a deep orange.

In May 1938 she had been hospitalized at the Boston City Hospital for 10 days. She was placed on a liquid syrup diet. The patient stated that the jaundice of her sclerae and skin decreased considerably. After her discharge she faithfully kept to her diet. However, three months later jaundice of the skin and sclerae is again increased. There was only slight pruritus. The patient did not have fever, chills or abdominal pain. Her stools again became clay-colored. Her urine was persistently deep orange. Although the jaundice varied in intensity, it was always present to some extent.

In January 1939 the patient noticed a yellowish discoloration and elevations along the creases of both palms. These lesions were progressive. In June 1939 she observed a small flat yellowish plaque along the inner canthae of both eyes. These plaques progressed rapidly involving the upper and lower eyelids. As far as the patient knew, there were no other yellowish spots, nodules or papulo-pustular eruptions on her body.

The patient complained of tiredness, weakness and listlessness. After a fall, three to four weeks before her admittance to the hospital, she had constant pain in the lower lumbar region and a sharp pain between the shoulder blades radiating around

* We should like to take this opportunity to express our sincere appreciation to Dr. J. Howard Means and Dr. Tracy B. Mallory of the Massachusetts General Hospital, to Dr. Chester Keefer and Dr. Franz Ingelfinger and Dr. Charles Branch of the Evans Memorial Hospital, to Dr. Gerald C. Leary, Resident Pathologist of the Pondville Hospital, Walpole, Massachusetts, and to Dr. Warren C. Hunter, Pathologist, University of Oregon Medical School, for permission to use case histories and anatomical material in this study.

the left chest wall to the left inframammary region. This pain, which developed in the evening, was not related to exertion, exposure to cold air or to eating of heavy meals. It was not relieved by rest. The patient had no headaches or sinus trouble. Her vision had been blurred. She has had no diplopia. She has had no ear or nose symptoms. Her teeth were in poor condition. For the previous two to three years she had a cough producing yellowish-whitish sputum. She had no hemoptysis or pleuritic pains, no exertional dyspnea, orthopnea, ankle edema or angina pectoris. There had been no recent nausea or vomiting. Her appetite had been improving. She took mineral oil every morning prophylactically. However, she was not constipated and had no diarrhea. Her stools were clay-colored, usually normally formed and not frothy or foul in odor. She had nocturia once or twice a night but no dysuria, hematuria or pyuria. Her urine was persistently deep orange. The patient complained of recent nervous feelings. She had noticed a tingling sensation in both hands and wrists for over a year.

Her habits were regular. She ate three times a day. She had meat in the form of liver and steaks as part of her antianemic diet, and fruit juices for liver trouble. She has had insomnia. Formerly she had worked as a night club hostess for three years and drank more than her share of liquor. She had taken practically no alcohol in the previous 18 months.

The patient's father had died of heart trouble at the age of 50; the mother of carcinoma of the uterus at 52. The mother's father had died of carcinoma of the stomach. The mother's sister had diabetes. There was no history of xanthomatosis in the family.

Physical examination showed a small, deeply jaundiced woman with temperature of 97° F. The skin over the arms was brownish colored. There was also a combination of lemon-yellowish and brownish jaundice on the palms. A small nodule was located in the right occipital region of the scalp. Rather extensive xanthelasmas were present in the inner canthi and along both the upper and lower lids. Those in the upper lid were more marked, measuring 3.5 to 4 cm. in length and about .5 cm. in width. They were also elevated 1 to 2 mm. above the level of the skin. The conjunctivae were not pale. Several small irregular nodules were found in the right inferior palpebral conjunctiva. The sclerae were deeply jaundiced. The fundi were not remarkable, and there was no lipemia retinalis. The mucosa of the hard palate was jaundiced. No yellowish nodules were seen on the buccal or pharyngeal mucosa. There was a small yellowish elevated nodule about 3 mm. in diameter over the ankle of the right foot. A small wide yellowish plaque of 12 mm. and another of pinpoint area were observed in the right antecubital space. No nodules were found on the extensor surfaces of the elbows and knees. There were slightly elevated yellowish deposits, a few mm. in width, along most of the flexor creases of both palms. These were most marked at the metacarpophalangeal creases of the thumb. In some interspaces they extended almost to the dorsum of the hand. The reflexes were normal.

The lungs were normal. The apex impulse of the heart was felt 9 cm. to the left of the midsternal line in the fifth interspace. The area of cardiac dullness was not enlarged by percussion. The rate was 76 per minute, and the rhythm was regular. No murmurs were heard. The vessels were not arteriosclerotic. The radials were equal and synchronous. Blood pressure 135 mm. Hg systolic and 85 mm. diastolic.

The abdomen was soft without tenderness or rigidity. The liver, markedly enlarged, especially on the right side of the abdomen, extended up into the left hypochondrium. The spleen was not definitely palpable but was enlarged by percussion. No other masses were felt.

Roentgen-ray examination: The liver was extremely enlarged. The spleen and kidneys appeared to be within normal limits. There was no roentgenological evidence of esophageal varices.

Laboratory data: Urine, amber color, cloudy, reaction acid, gravity 1.007, slightest possible trace of albumin, negative sugar, normal urobilinogen, rare red and white cells. Blood sedimentation rate was 86 mm. at the end of one hour by the Westergren method. Hemoglobin 69 per cent or 9.5 grams; red blood cells 3,210,000; white blood cells 11,450; color index 1.08; differential count showed 74 per cent polymorphonuclears, 1 per cent bands, 2 per cent eosinophiles, 1 per cent basophiles, 19 per cent lymphocytes and 3 per cent monocytes. The smear showed some anisocytosis, macrocytosis and microcytosis. The platelets appeared normal.

The patient was discharged from the hospital with a diet almost free of animal cholesterol and low in animal fats. Vegetable fats like olive oil and peanut oil were allowed.

January 12, 1940: This patient reported that she kept her diet. The jaundice seemed unchanged. *Liver:* Four fingers below the costal margin, firm and smooth surface. *Spleen* definitely enlarged and palpable two fingers below the left costal margin. Constant itching of skin. (Chemical analysis of serum, see table 1.)

June 1, 1940: The skin xanthoma did not change although the patient adhered rigidly to her diet. Liver enlargement not diminished. Spleen became larger, two fingers below the left costal margin. The patient complained about pain in her stomach two to four hours after she ate, which awakened her in the early morning hours. As she was already on a vegetarian diet, low in fat but high in carbohydrates, no special diet change was made. (Blood chemistry, see table 1.)

February 7, 1941: Gastrointestinal complaints unchanged. Liver and spleen enlargement unchanged. Jaundice as well as skin xanthomas not increased. (Blood chemistry, see table 1.)

July 22, 1941: Roentgenologic studies showed a double ulcer of the duodenum. Stool examination for occult blood slightly positive. Patient had had profuse vaginal bleeding the previous week. Gynecological examination: vaginal polyp and fibromatous uterus. (Blood chemistry, see table 1.) Cholesterol-free diet continued.

November 14, 1941: (Blood chemistry, see table 1.) Because of increasingly constant stomach pain, an exploratory laparotomy was performed by Dr. F. H. Clute (November 20, 1941) and revealed a double duodenal ulcer. It was not resected. At this time a *liver biopsy* was taken (figures 1 to 6). Postoperative course was uneventful. No bleeding.

January 7, 1942: Abdominal discomfort from the ulcer continued. The patient believed she had contracted an upper respiratory infection a few weeks before. She coughed and produced a fair amount of whitish mucous sputum.

July 25, 1942: Cough and sputum were less. Her main complaint now was the itching of the skin. Liver and spleen still enlarged. Jaundice and skin xanthomas unchanged. (Blood chemistry, see table 1.)

December 10, 1942: Patient had lost considerable weight (10 to 15 lbs.) in the past two weeks. She developed a high temperature running up to 103°, which continued from that time. Roentgenograms of the lung unfortunately were not taken.

January 16, 1943: The patient was hospitalized again because of her extreme weakness and high temperature. *Lungs:* over both lungs fine moist consonating râles were heard. No dullness. *Liver and spleen* were greatly enlarged. No ascites. No evidence of ankle edema. Xanthomas and jaundice unchanged. Spider veins were noted on several places of her skin. (Blood chemistry, see table 1.) The patient was believed to have pneumonitis. The sputum was not examined for tubercle bacilli. Roentgenograms of the lung were not taken. The patient became progressively weaker and died on February 27, 1943. Until her death, she was conscious and not in a hepatic coma (blood chemistry, see table 1).

Pathologic Report: The biopsy specimen received in December 1941 was wedge shaped and measured 1.5 by 1 by 0.8 cm. It included capsule and underlying liver

TABLE I

Lipid Analysis of Case D. L. M.

	Cholesterol free diet							Fever due to tuberculosis			Normal
	11-27-39	1-12-40	6-1-40	2-7-41	7-22-41	11-14-41	1-7-42	7-25-42	1-16-43	2-27-43	
Total cholesterol	1460.0 mg. %	1140	840	1040	670.0	870	830	444	258	death	150–260 mg. %
Free cholesterol	155.0 mg. %	406	250	300	310.0	135	134	99	137		40–70 mg. %
Cholesterol present as esters	1305.0 mg. %	734	590	740	360.0	735.0	696	345	121		70–75% of total cholesterol
Total phospholipids	2300.0 mg. %		1572					1000	1880		150–250 mg. %
Cephalin	30.0 mg. %										10–30 mg. %
Lecithin	2120.0 mg. %										140–220 mg. %
Total fatty acids	1970.0 mg. %										200–450 mg. %
Neutral fat fatty acids	0										0–250 mg. %
Neutral fat	0										0–250 mg. %
Bile acids	5 mg. %	8	6.44		3.4 mg.						0–2
Bilirubin	dir. 6.60 indir. 6.60		indir. 5.4 dir. 3.6		5.3 dir. 7.3 indir.					total 19.50	
Serum protein				8.6 tot. 6.0 alb. 3.6 glob.	6.5 tot. 4.1 alb. 2.4 glob.						
Phosphatase (Bodansky U)										10	1–4 μ
Blood sediment rate	1 hr. 86				98 1 hr.	1 hr. 115	1 hr. 125	1 hr. 54			

tissue. There was no gross thickening or irregularity of the surface. Many sections were made and each was entirely free of subcapsular fibrosis, a condition commonly seen in blocks of liver taken from the gall-bladder area. In each section between 50 and 100 portal areas could be readily counted. This afforded a fair and adequate interpretation of the underlying disease. Preparations of this size removed without trauma or coagulation are very much better than fragments extracted by needle biopsy.

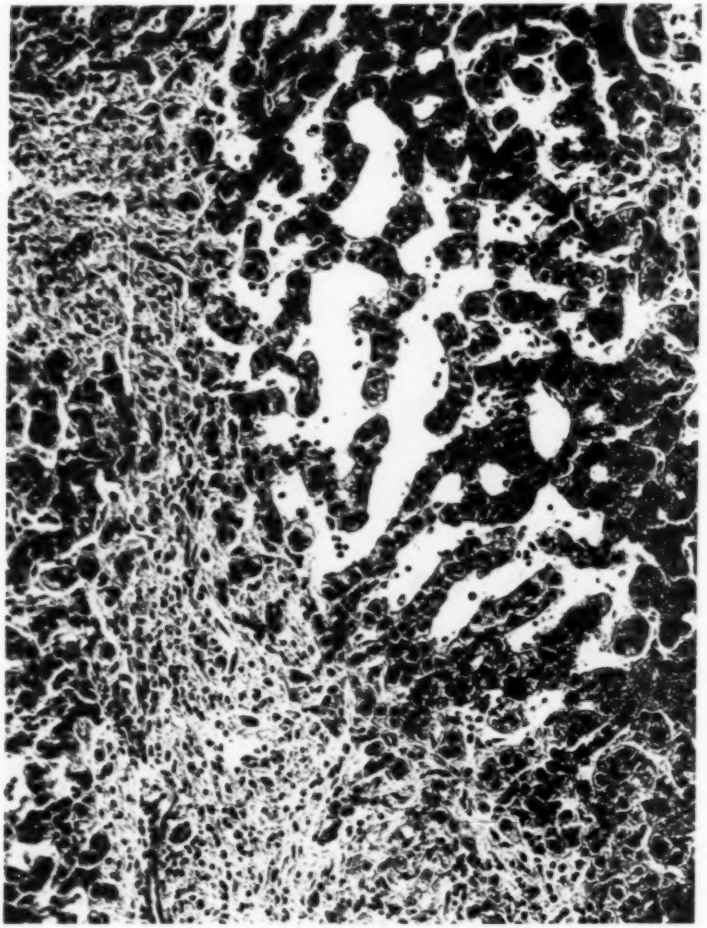


FIG. 1. Liver. This field was selected to show a portion of the peripheral zones of two lobules together with an inflamed and thickened portal area. It shows an extension of the inflammatory process into the lobule with compression of some sinuses and dilatation of others.

FIG. 2. Liver. This field was selected to show an inflamed and widened portal area. There is a rich cellular infiltration. There is an increase in inflammatory granulation tissue and there is an extension of this inflammatory reaction into the peripheral zones of the lobule. No bile ducts are visible in this field, but liver cells are so compressed that they resemble terminal cholangioles. The only suggestion of a portal vein is the presence of several compressed and slit-like endothelial lined spaces.

Microscopic Findings: The pattern of the liver was well preserved and all portal areas, lobules and central veins were easily identified. The pathological change was centered in the perilobular or portal connective tissue. This change involved all portal areas, but the lesions varied in size. No portal area in any of the sections could be considered normal. The lesion was characterized by a non-specific, subacute to chronic inflammatory reaction centered at the junction between portal area and

lobule (figure 1). It was characterized by a proliferation of fibroblasts, the formation of new capillaries, a light deposition of collagen and a variable infiltration of cells. These included neutrophiles, lymphocytes, monocytes, plasma cells, eosinophiles and very, very rarely, a multinucleated giant cell.

The small bile ducts so readily seen in the portal areas of healthy livers could not be identified. The lymphatics and terminal branches of the portal vein were com-

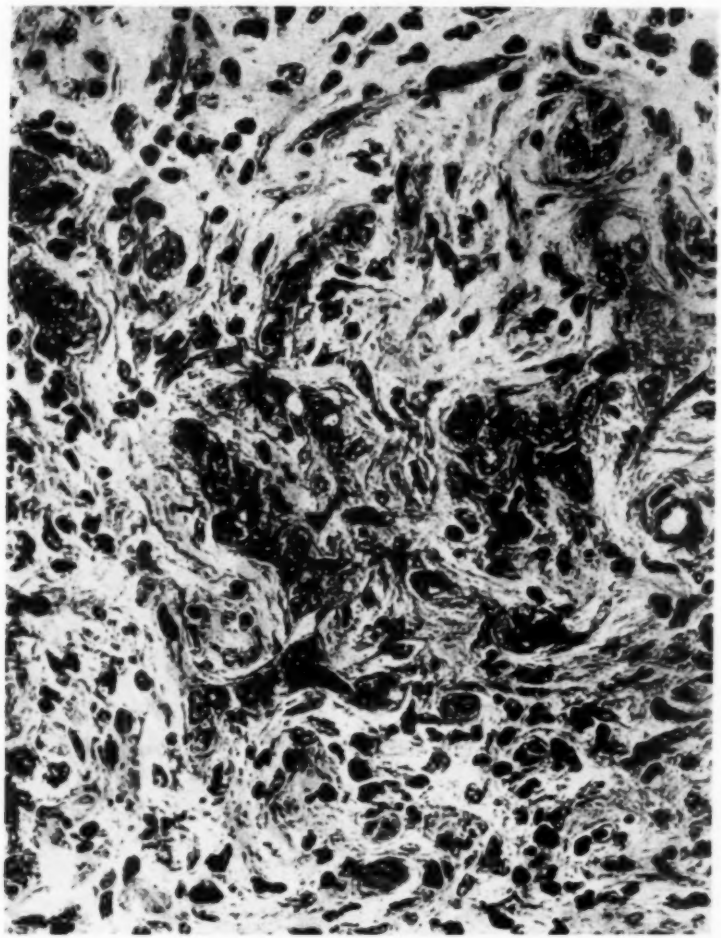


FIG. 3. Liver. This is a higher power magnification of a field at the periphery of a lobule. It shows the increase in fibrous tissue extending into the lobule surrounding and compressing cords of liver cells. Neither the sinuses nor the sinus endothelium is recognizable. The sinuses are now filled with inflammatory granulation tissue.

pressed, narrowed and in areas obliterated by inflammatory granulation tissue (figure 2). The small arteries were unchanged.

This inflammatory reaction originating in and radiating out from the portal areas led to a variable and often irregular expansion of the perilobular connective tissue. The picture suggested a spilling over of inflammatory tissue from the portal areas into the peripheral zones of the lobules. The lines of demarcation between portal connective tissue and lobules were poorly defined because of this infiltration of inflammatory granulation tissue into the bordering parenchyma.

In the beginning the reaction is centered about the terminal bile ducts and is confined to the portal areas. From here it spreads into the most peripheral portion of the lobule by infiltrating along the perisinusoidal spaces of Dissé. In this manner liver cells, singly and in cords, become bordered by inflammatory granulation tissue (figure 3). The sinus at first narrowed by this increase in fibroblasts later disappears. At this stage the histological picture suggests a solid wedge of granulation tissue separating and compressing intact and broken cords of liver cells. In the early stages the marginal liver cells remain unchanged, but later when they become engulfed in fibrous tissue they show a series of regressive changes. Some of them swell to twice their normal size and accumulate vacuoles in their cytoplasm. In some the cytoplasm becomes granular and eosinophilic. Other liver cells accumulate bile and still others show necrosis and disintegration.

Signs of liver cell regeneration were found in the peripheral zones of lobules (figure 4). This was shown by the presence of mitotic figures. The very few small bile ducts that were visible in the portal areas were so compressed and flattened that they resembled solid cords of endothelial cells. There were no leukocytes or bile casts within the lumina of any of these bile ducts. The junction ducts or canals of Hering, so difficult to see in a normal liver, were accentuated by the ingrowth of inflammatory granulation tissue.

Bile stasis was a striking finding. First, there were large and small casts of inspissated bile in the canaliculi of collapsed and compressed cords of liver cells. Secondly, there were coarse clumps of bile in liver cells bordering the portal areas. There was no bile retention within the central zones of the lobules. This seemed paradoxical, for this is the common site of bile retention in simple extra-hepatic biliary obstruction.

The sinuses adjacent to the portal areas were sometimes dilated and sometimes compressed. The lining endothelial cells were, for the most part, inconspicuous, but here and there an isolated endothelial cell was laden with lipoid. The central veins and sublobular veins, with few exceptions, showed no sign of inflammatory granulation tissue (figure 5).

Rarely the inflammatory reaction in the portal area cut deeply into the lobule and in one field a continuous track of granulation tissue could be traced from the portal area to the central vein (figure 6). The type and extent of the cellular exudate warrant a more detailed description. In some fields the cellular infiltration was minimal. In other areas, it so dominated the field that it obscured completely the underlying granulation tissue. One field showed nests of polymorphonuclear leukocytes, another was dominated by lymphocytes and histiocytes.

To summarize the overall picture, it may be said that the liver was the seat of an active, subacute to chronic inflammatory reaction centered in the portal areas. This was characterized by an increase in inflammatory granulation tissue with a corresponding widening and lengthening of the portal connective tissue. There was a tendency for portal areas to unite and to form thin barriers of perilobular fibrosis. There was bile stasis within the lobules and many of the sinuses were narrowed or blocked. The nature of the reaction may be distinguished from the changes seen in obstructive and cholangitic biliary cirrhosis though its distribution is similar to that

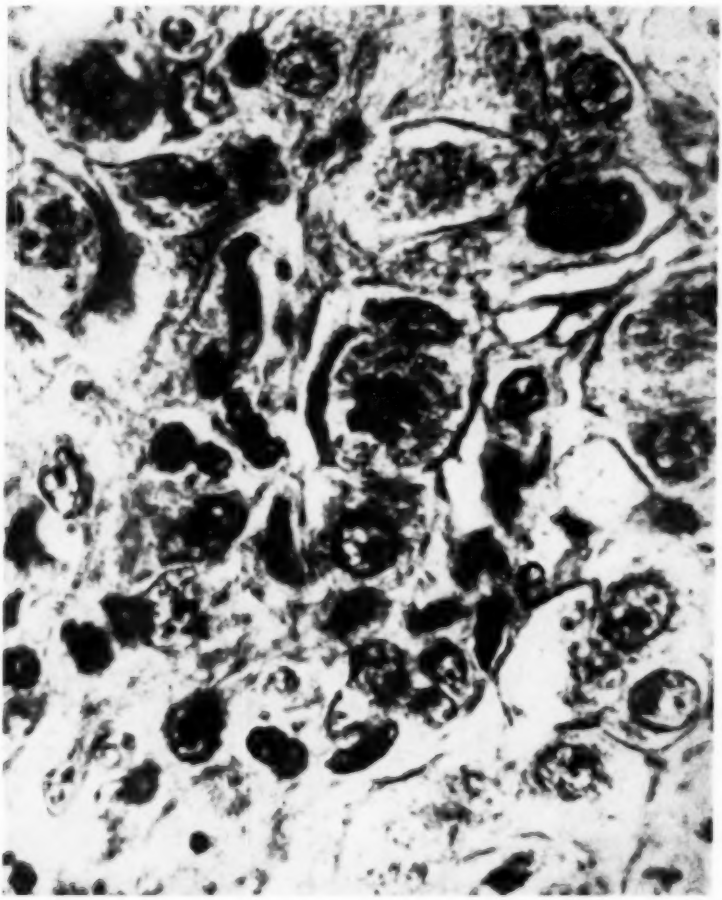


FIG. 4. Liver. This field was selected to show a liver cell in mitosis. The cell is swollen and larger than those bordering it. The nuclear membrane is lost and the chromatin forms a coarse cluster in the center of the cell.

of both of these forms of cirrhosis. Because the lesion is centered about the terminal bile ducts and because it is characterized by an inflammatory process, and particularly because at the present time the etiology remains obscure, the name pericholangiolitic biliary cirrhosis is suggested.

Autopsy Findings: The liver was large, uniformly granular and bile-stained. On section, the freshly cut surface showed a lobular, but coarse, pattern. There was absolutely no suggestion of any type of extra-hepatic biliary obstruction and no lipoid was seen in any part of the biliary tract.

Microscopic Findings: The histology of the liver was now much more complex than in the biopsy taken 14 months previously, for now the pathology was much older and it was complicated by a very recent and terminal miliary form of tuberculosis.

The pattern of the liver was badly distorted. The portal areas were wide, branching, irregular and rich in fibrous tissue. They reached out into the lobules

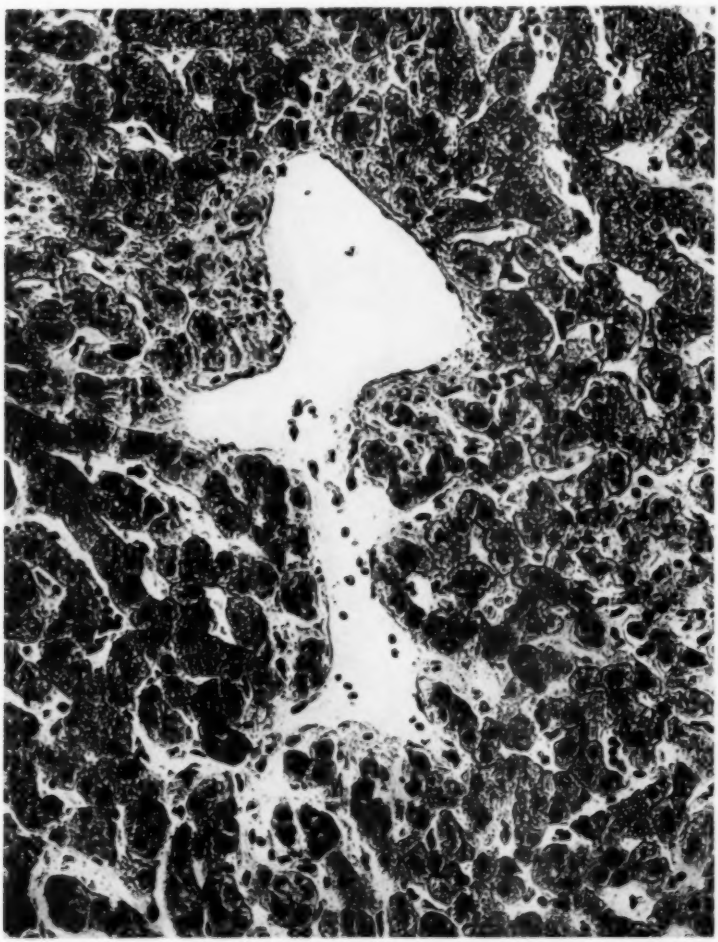


FIG. 5. **Liver. This field was selected to show the junction of a central vein with a sublobular vein. The vessels are dilated and contain few cells. The endothelial cells lining the vessel are flat and inconspicuous. The surrounding liver cells are orderly and bear a normal relationship to sinus endothelium. There is no trace of inflammation. Fields of this sort were common and stood out in sharp contrast to the changes going on in the periphery of the lobule.**

and broke them into smaller and irregular nodules. There were nodules of regenerated liver cells. The liver parenchyma was edematous and delicate fibrous strands extended far along the sinuses into the lobules (figure 7). Some of the sinuses were collapsed, some were distended with blood; some contained nests of endothelial cells laden with lipoid. Many of the liver cells showed hyaline degeneration. Lastly, there were tubercles in every field.

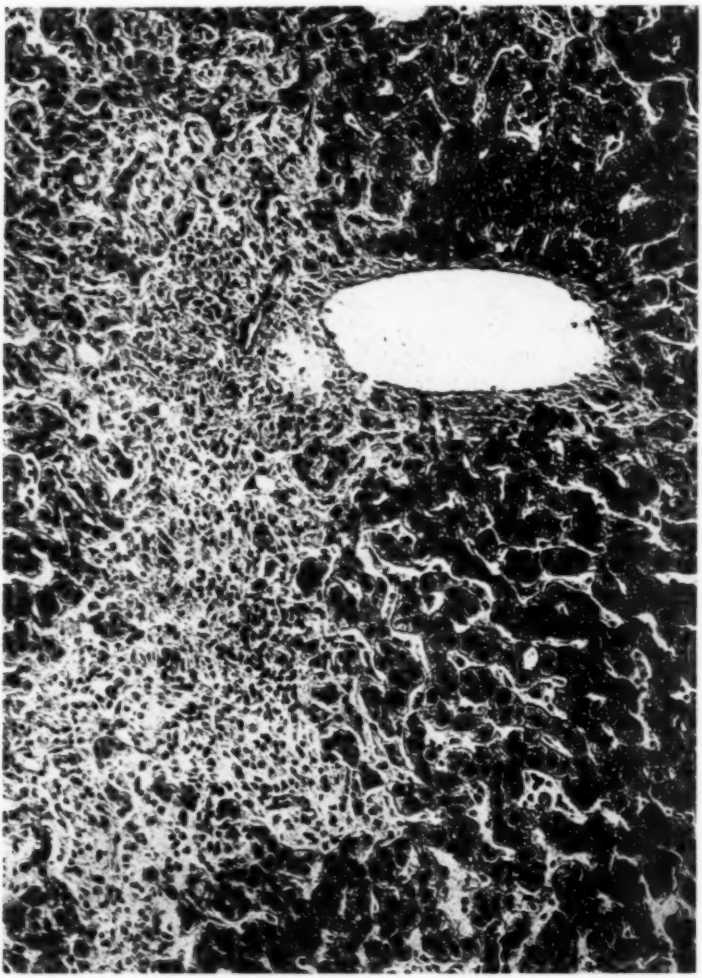


FIG. 6. Liver. This field was selected to show the extension of an inflammatory process from the adjacent portal area out to the edge of a central vein. The central vein itself is dilated and most of the surrounding lobule is free of pathology.

The large size of the liver, the diffuse and extensive fibrosis, the intracellular bile stasis and the still active inflammatory reaction in the portal areas offered a very complex histological picture. It is interesting to compare the liver now with the biopsy studied months earlier. Common to both is the bile stasis, the hyaline degeneration of liver cells (figure 8), and the widening of the portal areas. In the biopsy, the lobular pattern was retained, at the time of autopsy there was little of the original pattern recognizable. The large bile ducts at the hilus of the liver and

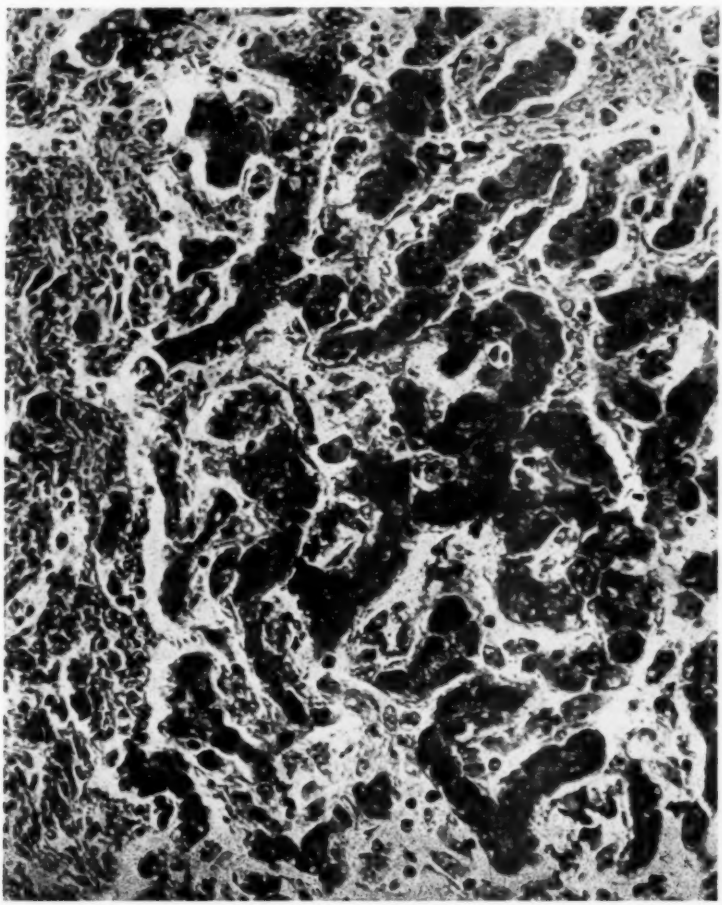


FIG. 7. Liver, at the time of autopsy. This field was selected to show a portion of the peripheral zone of a lobule or nodule of liver cells bordering an area of fibrosis. The cords of liver cells are tortuous and widely separated. The sinuses contain large lipoid-laden histiocytes. There is a moderate increase in perisinusoidal collagen. The sinuses are collapsed and poorly defined.

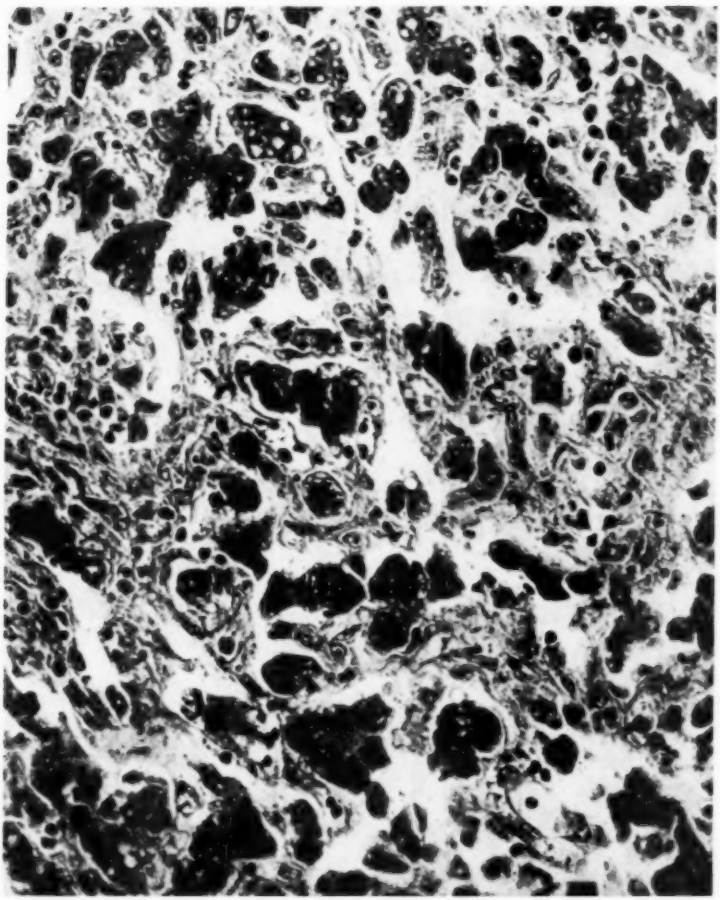


FIG. 8. Liver. This section is from the liver at the time of the autopsy. This field was selected to show a group of liver cells, adjacent to a portal area, containing large deposits of coarse, eosin-staining hyaline. The cords of liver cells are broken up and the sinuses are collapsed by perisinusoidal edema and fibrosis.

radiating throughout the liver were collapsed and empty. In none of the intrahepatic bile ducts were xanthoma cells demonstrable. The classification of this type of cirrhosis, when seen for the first time in its end stages at the autopsy table, is puzzling and often uncertain. It is difficult to realize that a lesion that begins in the portal areas can lead to such destruction.

Clinical Comment on Case D. L. M.: The patient exhibited during the first two years of observation the typical characteristics of xanthomatous

biliary cirrhosis suggested by Thannhauser and Magendantz: (1) Skin xanthomas (xanthelasma of eyelids, tuberous xanthomas on elbows, xanthomas of the creases of the palms). (2) Enlarged liver and spleen. (3) Obstructive type of jaundice with bilirubin giving the direct and indirect van den Bergh reaction. (4) Extremely high values in the total cholesterol (1460 mg. per cent, about 85 per cent present as esters) as well as for lecithin (2120 mg. per cent, about *10* times normal). (5) The serum is transparent despite the high cholesterol and lecithin content. Neutral fat is not present in measurable amounts.

Thannhauser [24] suggested that the accumulation of cholesterols and lecithin in the serum at the outset of xanthomatous biliary cirrhosis may be caused by an increased formation of these substances in the liver by a functional disturbance of the liver cells. Histological examination of this patient's liver had already revealed in the early stages fibrotic changes in and around the finest bile capillaries. At this point it seems appropriate to consider which of three possibilities is concerned with the pathogenesis of the disease: (1) whether the assumption of an increased formation of cholesterol and lecithin in the liver is justified, (2) whether these substances are retained in the serum only by an impaired elimination due to fibrotic obliteration of the finest bile capillaries; or (3) whether both processes, namely increased formation and retention cause the high values for cholesterol and lecithin in the serum. The clinical and laboratory findings during almost three years of observation of this unique case provide the basis for such a discussion. An increased formation of cholesterol and lecithin may be indicated by the following findings.

1. The total cholesterol of the serum, 1460 mg. per cent on an unrestricted diet, could not be reduced lower than about 800 mg. per cent cholesterol and 1000 mg. per cent lecithin on a diet free of animal cholesterols and fats. These high cholesterol and lecithin values were maintained during the period of diet treatment for two and a half years (see table *2*). This observation suggests that an excessive endogenous production of cholesterol and lecithin persisted while the exogenous quota of animal cholesterol supplied by food was meanwhile almost completely restricted.

2. The cholesterol concentration in the serum decreased markedly and was almost normal in the final period of the disease possibly because an intercurrent tuberculous disease with miliary dissemination in the liver caused the replacement of some of the liver parenchyma. The obliteration of the finest bile capillaries producing the retention continued during this terminal phase, but not enough functioning liver tissue remained to maintain the formerly increased cholesterol formation. One may object to such an explanation, referring to experiences where the total cholesterol values are always very low in cases of hepatic failure, such as in acute yellow atrophy of the liver and in the last stages of a decompensated portal cirrhosis. This

patient, however, never had hepatic failure nor hepatic coma but died as a result of tuberculosis of the lung and disseminated tuberculosis.

3. The cholesterol and lecithin level in the serum in complete obstruction of the common bile duct, resulting from occlusion by a stone, carcinoma or fibrosis after a surgical accident, is never as extremely high as in xanthomatous biliary cirrhosis, that is, values as high as 1450 mg. per cent total cholesterol and 2120 mg. per cent lecithin observed in Mrs. L. M. and in the first stages of other cases of xanthomatous biliary cirrhosis in this paper. The early liver biopsy of Mrs. L. M. showed obliterative changes in the finest bile capillaries in some areas of the liver. It seems, however, unlikely that the fibrotic obliteration of some cholangioles in parts of the liver at the beginning of the disease should result in a much greater retention of cholesterol and lecithin than is observed in a case with complete occlusion of the common bile duct.[25] With regard to Mrs. L. M., bile was certainly always produced, and that a fair amount reached the intestines was demonstrated by the presence of urobilin and urobilinogen in the feces and urine during the course of the disease and by the aspiration of dye-stained bile from the patient's common duct during the operation. As the disease progresses, the fibrotic changes of the cholangioles involve greater areas of the periportal space. Thus the retention of bile is certainly increased, but the cholesterol and lecithin values in the serum decrease the more the liver parenchyma is replaced by fibrotic tissue. It may also be noted that the bilirubin values in the serum at the outset were never outstandingly high and definitely not as elevated as those observed in complete blocking of the common duct. The level of bilirubin in the serum of these patients does not parallel the increase or decrease of cholesterol and lecithin.

4. Skin xanthomas were already developed in this case in the early stages of the disease (first year) at a time when the bilirubin was only moderately increased. As far as can be ascertained from the history of the patient, skin xanthomas did not precede the jaundice. Patients with complete obstruction of the common bile duct by stone, carcinoma or surgical obliteration exhibit a severe grade of jaundice, a moderate increase of cholesterol and a slight increase of lecithin, but skin xanthomas do not appear.[25, 26] The rare instances of skin xanthoma reported [18] after surgical obstruction seem rather exceptional. In these cases the skin xanthoma disappeared as soon as the bile flow was restored whereas in xanthomatous biliary cirrhosis, the skin xanthomas persist despite the fact that bile is constantly excreted in the intestines.

The clinical and laboratory data collected during the period of observation favor the suggestion of Thannhauser [24, 27] that the marked accumulation of cholesterol and lecithin at the beginning of xanthomatous biliary cirrhosis is probably not only the result of a retention of bile but also the consequence of an imbalance of increased cholesterol and lecithin production and an inadequate excretion of these substances. The explanation of the finding of excessively high cholesterol and lecithin as the result of hyperproduction of

cholesterol and lecithin in xanthomatous biliary cirrhosis remains a hypothesis. Such a hypothesis is, however, supported by the laboratory findings and by a comparison of this and other cases of xanthomatous biliary cirrhosis with other clinical syndromes where the obstruction and bile retention are complete and the only etiological factor. In the cases of complete obstruction the lecithin and cholesterol content of the serum is by far not as high as in xanthomatous biliary cirrhosis despite the fact that in this disease the bile flow is always patent.

Case 2. T. P., 38 year old female, of Finnish descent.

Past History: Patient is married and has two children. She was always well until she had menstrual disturbances in January 1938 when she was operated on for a fibroma. After leaving the hospital in February, she felt an itching all over her body. One week later she had attacks of abdominal pain and noticed that her skin was jaundiced. She did nothing until May 1938 when she saw a doctor for her jaundice, which has never since completely cleared. Her appetite was good. She never had chills or fever.

First Admission to the Massachusetts General Hospital, Boston, March 20, 1940. Jaundiced patient with no complaints. Heart: Normal in size, no murmur. Blood pressure 108 mm. Hg systolic and 79 mm. diastolic. Liver enlarged, spleen not felt. Laboratory findings: Bilirubin 6.9 biphasic reaction. Prothrombin time 29.1 (normal 21.0). Hinton test negative. Discharged to the out-patient department with the diagnosis, "Biliary cirrhosis" and jaundice. Transferred to Surgical Department, May 19, 1940. Physical examination showed the same findings of an enlarged liver and chronic jaundice. The patient was also seen at the dental clinic for dental bleeding. Laboratory findings: Bromsulfalein test 80 per cent retention. Non-protein nitrogen 18 mg. per cent. Total protein 7.1 gm. Bilirubin: van den Bergh test 13.0 mg. biphasic.

Exploratory Laparotomy May 29, 1940 (Dr. A. W. Allen). No fluid in the abdomen. Spleen was three times larger than normal. Liver moderately enlarged. Surface not scarred or nodular but slightly greener than normal. Head of the pancreas normal, but the pancreas was thickened. Bile duct was identified. The common duct was probed. No stones found above and below or toward the gall-bladder. Dark bile could be seen coming from the gall-bladder. No stones. Bile duct roughly 7 mm. in diameter. Comment: After careful exploration no evidence of stone in the duct or gall-bladder.

Liver Biopsy. (See page 139.)

Second Admission: Had pain on her left side, no loss of weight. Flank pain on both sides. Jaundiced yellow sclerae. Bleeds from the gums very easily. Some brown pigmentation on her face and abdomen. Laboratory findings: Non-protein nitrogen 29 mg. Total protein 5.8 gm. Bilirubin 9.7. Biopsy of skin: No evidence of hemochromatosis.

Patient was seen in the out-patient department and was constantly jaundiced. Bilirubin 28.5 biphasic. Prothrombin time 19. Sodium 139.7 mg. per cent.

Third Admission, March 1941. Between January and March 1941 innumerable xanthomas developed on the patient's face, arms, elbows, legs and feet. The creases of the palms showed many flat xanthomatous lesions, firm and yellow, linear and rounded in character.

Roentgen-ray of the esophagus and stomach did not reveal esophageal varices. Prothrombin time taken several times was normal.

Patient was now in the out-patient department repeatedly. The clinical picture did not change.

Fourth Admission, May 1941. The patient was hospitalized because of an acute cellulitis of the left leg. After she recovered, one of us was allowed to see her (Thannhauser) through the courtesy of Dr. James H. Means and to examine the serum for the various lipids. The skin, especially around the neck, was dark brownish. The jaundice was of moderate grade. Liver was four fingers below the costal margin. The spleen was large and firm. There was no ascites. Plain xanthomas were noticed around the eyelids and both creases of the hands. The tuberous form of xanthoma, firm and of a yellow carotene color, appeared on her face, neck, elbows, lower arms and legs. Laboratory findings: Van den Bergh 7.9 direct; 9.6 indirect. Lipid partition (see below). (Figure 9.)

FIG. 9. *Case 2.* T. P. Diffuse brownish pigmentation. Jaundice. Xanthelasma of the eyelids. Tuberous xanthomas of face and neck. Xanthomatous involvement of the creases of both hands.

Fifth Admission, April 1944. Patient admitted with bleeding from esophageal varices. No history of alcohol intake. The past few months the patient had felt exhausted but did her housework. About two weeks before her admission the stools became tarry. The day before admission she had a peculiar sensation below the sternum and vomited a tablespoon of bright blood. Her general appearance was the same as previously. The liver and spleen were enlarged. No ascites. Laboratory findings: Non protein nitrogen 35. Bilirubin 6.6 direct; 9.3 indirect. Total serum protein 5.3 gm. Albumin 2.7. Globulin 2.5 (April 5, 1944). Hemoglobin 3.5 gm. Red blood cells 1,500,000. White blood cells 12,200. Polymorphonuclears 84 per cent. Small lymphocytes 9 per cent. Monocytes 0. Platelets decreased (April 22, 1944). Hemoglobin 49 per cent. Red blood cells 3,200,000. Stool: guaiac ++++.

Sixth Admission, Dec. 16, 1944. Esophageal bleeding. General appearance unchanged. Laboratory findings. Hemoglobin 5.0 gm. Red blood cells 2,200,000. Polymorphonuclears 90 per cent, lymphocytes 6 per cent, monocytes 2 per cent. Urine, specific gravity 1.106. Albumin +, bile +++. No tyrosine or leucine crystals. Patient died December 18, 1944.

TABLE II

Lipid Analysis of the Serum of Patient, T. P.
The serum is *transparent* and not milky

	May 12, 1941 Analysis—Research Laboratory Boston Dispensary	April 5, 1944 Analysis—Mass. General Hospital	Normal
Total cholesterol	1115 mg. %	368 mg. %	150–260 mg. %
Free cholesterol	143 mg. %		40–70 mg. %
Cholesterol present as esters	972 mg. % (87% of total cholesterol)	110 mg. % (29% of total cholesterol)	70–75 mg. % of total cholesterol
Total phospholipids	2240 mg. %		150–260 mg. %
Cephalin	50		
Lecithin	1710	625	
Serum lipase	Normal		
Diastase	Normal		
Acid phosphatase	Normal		
Alkaline phosphatase	27.5 Bod. U		

Analysis of Liver Tissue after Autopsy, Dec. 19, 1944

		Normal % of dry weight
Total cholesterol	2.2%	2.0 –2.6%
Free cholesterol	1.07%	0.44–0.55%
Cholesterol present as esters	0.13%	1.5 –2.15%
Total phospholipids	7.0%	9.0 –11.0%
Cephalin	5.2%	3.0 –5.5%
Lecithin	1.8%	3.0 –6.0%
Total fatty acids	13.25%	8.0 –13.0%

Pathological Report: The biopsy specimen from the liver May 29, 1940 of this patient showed a subacute to chronic inflammatory reaction in every portal area. In addition there was severe bile stasis within the lobules. The inflammatory reaction was confined to widened but well demarcated portal areas. Junction ducts were numerous, but small bile ducts, in contrast, were difficult to find. Neither bile nor leukocytes were seen within any of the bile duct lumina. Liver cells bordering the portal areas showed regressive changes. No xanthoma cells were found in any of the portal areas.

The histological findings at the time of the autopsy, December 18, 1944, were quite different. The uniform distribution of the early inflammatory lesions was replaced by a very patchy disorderly and far advanced perilobular fibrosis. There was little cellular exudate and in these wide communicating bands of fibrous tissue there were very few small insignificant collapsed empty bile ducts. In some areas whole lobules had been destroyed and in other areas the structure of the original lobules was little changed. There was a diffuse and severe bile stasis, most marked in distended canaliculi bordering zones of fibrosis. An interesting finding was the accumulation in some of the dilated sinuses of endothelial cells containing lipoid, but it must be emphasized that no xanthoma cells were found in any of the bile ducts. Scattered throughout the liver and complicating this picture of fibrosis were small nodules of regenerated liver tissue.

The diagnosis of the biopsy specimen was that of chronic pericholangiolitis with beginning pericholangiolitic biliary cirrhosis. The diagnosis of the liver at the time of autopsy was difficult and an accurate interpretation of the pathogenesis of this type of cirrhosis without the earlier biopsy would have been extremely hazardous.

Clinical Comment: Patient T. P. presented the following picture during the course of the disease: (1) Continuous jaundice (five years); (2) skin xanthoma (plain and tuberous type for three years); (3) enlarged liver and spleen; (4) extremely high total cholesterol as well as lecithin values in the serum (1115 mg. per cent for total cholesterol and 1710 mg. per cent for lecithin); (5) transparent serum despite the high cholesterol and lecithin content. These features correspond with those of xanthomatous biliary cirrhosis. In the last phase of the patient's illness the values for total cholesterol as well as for lecithin decreased, probably because of the progressing cirrhosis which also produced portal obstruction. Varicose veins of the lower esophagus caused considerable bleeding and led to her death. It is evident from the exploratory laparotomy and from the liver biopsy four years previously that the disease did not start with extensive changes of the liver parenchyma nor with obstruction of the common bile duct. After an insidious onset, jaundice of moderate grade was the first symptom lasting the entire five years of illness. Skin xanthomas were noticed by the patient subsequently two years later. The skin xanthomas persisted even in the final stages although the cholesterol values of the serum decreased considerably because of the progressing cirrhosis. It may, however, be noted that the concentration of cholesterol and lecithin in the serum remained higher than normal until the patient's death.

Case 3. Mrs. P. H., 48 year old housewife, was referred by Dr. Edward S. Medoff to the J. H. Pratt Diagnostic Hospital on April 27, 1941.

Chief Complaint: Skin trouble and jaundice.

Present Illness: Seven or eight years ago this woman first noted the occurrence of dermatographia. If she marked her skin with a match, as in making initials, the contacted area became red and raised, lasted for several minutes and disappeared.

In the fall of 1937 she noticed the onset of weight loss and had a generalized tired feeling. After moderate exercise she felt all in and had no strength. Weight loss of about two pounds a week continued. When these symptoms first appeared, she weighed approximately 134 pounds and within a period of several months, she lost 30 to 40 pounds. In January and February of 1938, she felt a generalized itching, so marked and distressing that she visited a doctor in March. The physician, who had known her for a long time, was surprised to see her yellow skin and told her she had jaundice. A Wassermann test was negative. She now had become quite nervous and irritable. Since she received no relief from the physician's medication, she saw another doctor (1938). At this time she noticed raised areas on the palmar surfaces of both hands. Small nodules appeared in the crevices of the skin and at the flexion point of the fingers, gradually involving the entire hand. The hands were quite swollen, and she was unable to clench her fist. The raised areas were smooth, white at the beginning but later turning yellow. These persisted and about 1939 similar lesions became visible around the eyes and then seemed to spread everywhere. These smooth, raised yellowish-orange lesions were observed around the nose and the neck as far down as the collar bone. They covered the elbows as well as the flexor surface of the forearm, the anterior aspect of the knees, the posterior aspect of the ankles, the skin over the Achilles tendon, and the toes and hands. The rectum and the buttocks also showed these nodules. For about two years there was no particular increase or change in their aspect. However, if the patient happened to scratch one of them severely, it bled and exuded a yellowish fatty material for a short time.

There had been no marked change in the past year or two in the loss of weight, weakness, nervousness and continuous jaundice. In November 1940 the patient had four teeth removed with profuse gum bleeding. In December 1940 her physician did not advise a blood transfusion for the anemia incurred from the blood loss but gave her instead iron pills by mouth, which, according to the patient, had rebuilt her blood.

In the past four months her complexion had become much darker. Within the last two months blister-like lesions had developed over the face, nose and legs. Her weight was now 83 pounds in contrast to 91 pounds the previous year. Her appetite remained good. Sometimes she had considerable abdominal distention with eructations of gas, but this had been noted for a number of years. She had had no other pain or discoloration of the skin prior to her present illness. Since the itching was now quite marked and the skin deeply pigmented, she entered the hospital for further diagnostic studies.

FIG. 10. *Case 3.* P. H. Severe jaundice. Plain xanthomas (xanthelasma) around both eyes. Plain xanthomas in the supraclavicular fossae. Tuberous xanthomas of the face and neck.

Family History: The patient's father had died at the age of 78 of a shock; her mother at 72 of pneumonia. Her mother had had 16 pregnancies. Two were stillborn, and eight other children died in infancy. The patient has two brothers and three sisters living and well, none of whom have exhibited any disease or skin dis-

coloration like those of the patient. There was no history of tuberculosis, cancer, diabetes, cardiac or renal disease.

Marital History: Married twice, the first time 27 years previously. After eight years, her husband was killed in an automobile accident. They had one child, a boy, now 26 years old. She married a second time 17 years ago; her present husband, a sheet metal worker, is living and well.

Personal History: She was born in New Hampshire. Her work had always been of a domestic nature. Habits have been good. Diet adequate. As a result of her present illness the patient was advised to decrease her fat intake, but she still ate a little butter.

Past History: General health has always been excellent. The patient has had the usual childhood diseases with no past sequelae. She stated that she is said to have had malaria at the age of eight and remembers having shaking chills then. Has had no operations and no serious injuries.

FIG. 11. *Case 3.* P. H. Plain and tuberous xanthomas of both palms in addition to the xanthomatous involvement of the creases.

Systemic Review: Head—no headaches. Her teeth have been bad for a number of years, at least eight or ten. Her gums bleed quite easily, more noticeably so during the last few years. Her vision has been good. She has had no difficulty in hearing, no earaches. No glandular swelling of the neck. Cardiorespiratory: No substernal pain, precordial distress. In the winter time she has a cough. Gastrointestinal: Appetite has always been good. Bowel movements fairly regular. She takes a laxative occasionally. In the past two years her stools have been of different colors—at times black as tar or yellow, and sometimes yellow streaked or brown. She states that the stools are very greasy "as if you had thrown in a cup of grease." In the

past two weeks she has felt a slightly irritated area posterior to the rectum, especially when sitting on a hard chair. Genitourinary: Patient has always drunk much water and voids extensively. Since the presence of the jaundice, the color of the urine has been quite brown. No dysuria, pyuria, or pain simulating renal colic. Menstrual: Until onset of the present illness periods were quite regular but are no longer so. The last period was one month ago, and the previous one five months prior to that. The amount of flow has been decreased during the past two years. Sometimes she has clots. No dysmenorrhea. Skeletal: For the past two years she has had difficulty in kneeling, that is, pain in the knees on marked flexion. She knows of no swelling of the painful joints. Allergy: No manifestation. Diet: During the past two to three years the patient has been trying to decrease the amount of fat intake.

Physical Examination: On admission, temperature 98.6°. Pulse 80. Respirations 20. Weight 83½ pounds. Height 5 feet 4 inches.

FIG. 12. *Case 3.* P. H. Tuberous xanthomas on elbows and trunk.

The patient is a slight middle-aged woman, who appears much older than her years. She is mentally alert and quite jolly. The skin is deeply yellow and pigmented. The pigmentation is much deeper over the chest and abdomen. Another striking finding is the conspicuous xanthomatous lesions of the skin. These lesions include extensive xanthelasma, quite smooth and yellow-orange in color, around the eyes, involving the upper lids more extensively than the lower ones. Several single papillar lesions, slightly yellow in color are found on the face as well as inside the nasal cavities bilaterally. On the lateral aspect of the neck, at the collar bone, are two (bilateral) areas of smooth slightly raised xanthomatous deposits (xanthoma plana).

Similar xanthomatous lesions appear on each flexor aspect of the forearm. Along the elbow are raised tuberous lesions which are nodular and easily moved about. Extensive nodular xanthomatous lesions cover the palmar surface of both hands. The inferior aspect of both breasts at the points of approximation to the thorax show a linear deposition of xanthomatous material. On the anterior aspect of the knee are tuberous xanthomatous lesions, also similar ones between the toes, and several on the dorsum of the feet. Numerous tuberous xanthoma also occur on the knuckles of the hands, the region of the heel, and on the skin over the Achilles tendon. Widely dis-

FIG. 13. *Case 3.* Tuberous xanthomas of the patellas and lower legs.

persed xanthomatous nodules are found over the buttocks and there is a band of xanthomatous tissue around the anal orifice. There are also tiny single, yellowish, smooth areas over the back and occasional xanthomatous nodules over the entire body. There is marked icterus of the sclerae and the buccal membrane including the pharynx. As already mentioned, the skin is deeply jaundiced everywhere. The hair on the head is plentiful but graying. Eyes show no undue prominence. Pupils are of moderate size and round. The left pupil is somewhat larger than the right but both react well to light and to accommodation. Extraocular movements well carried out. No nystagmus.

The fundi show the discs to be well outlined as are the retinal arteries and veins. There is a suggestive yellowish tinge to the fundi. No hemorrhages or exudates noted. Nose: In the right nares there is a projection, but it cannot be said yet whether it arises from the septum or from the concha. No bleeding points of the mucous membranes were observed. Mouth: The tongue protrudes in midline without tremor, is slightly coated and fairly well papillated. Lower teeth are dirty and carious; several upper ones have been removed. The pharynx is icteric. Tonsils are small. No post-nasal discharge. Ears: The hearing is good. No mastoid tenderness. Sinuses: There is no tenderness over the maxillary sinuses. Neck: No glandular enlargement, neither is there generalized glandular enlargement. Thyroid: Not enlarged. Trachea in midline. Chest: The breasts are soft, no nodules, no tenderness. Lungs: Expansion good and equal on deep percussion. Lungs resonant throughout. On auscultation no râles are heard. Breath sounds are vesicular. Heart not enlarged, left border dullness being 8 cm. from the midline in the left fifth interspace. Heart sounds are loudest at the fourth interspace just lateral to the border of the sternum. Heart rhythm is regular. Blood pressure 160/80 in the right arm. Radial pulse regular and equal. Abdomen: Rather protuberant. The patient states that her umbilicus is now somewhat firm, this being unusual; she also thinks that the configuration has changed in the past year or two. In the left upper quadrant is a small mass which on palpation is found to be a firm spleen, extending a hand's breadth below the costal margin. The liver is easily palpable, firm, nontender, and also extends one hand's breadth below the costal margin in the midclavicular line. No other masses are felt. No tenderness. Extremities: no cyanosis of the nail bed; no ankle edema. Skeletal: No pain or limitation in movement of any of the joints except the knee joints. Patient cannot flex the left shank on the thigh, the angle of limitation being approximately 45 degrees. No swelling, no tenderness or increased heat in any of the joints. The patient also cannot completely flex the fingers because of the xanthomatous lesions. Neurological: Cranial nerves are intact. No motor or sensory disturbances. Reflexes are active and equal.

Laboratory Data: Urine, on admission, amber color, very slightly cloudy, alkaline reaction, specific gravity 1.009, slight trace of albumin, no sugar or urobilin, normal urobilinogen. Bile showed a three plus reaction. Sediment showed 1 to 3 red cells per high power field, less than one leukocyte per high power field. Scattered epithelial cells, many bacteria; one small clump of pus was seen.

Blood on admission: 71 per cent hemoglobin, 3.69 million red blood cells with color index of 0.96. White blood count 9,400 with 15 bands, 60 polymorphonuclears, 2 eosinophiles, 3 basophiles, 16 lymphocytes, 4 monocytes. Smear showed much anisocytosis, platelets appeared normal. Blood fragility tests: Control: hemolysis began at 0.42, it was complete at 0.32; the patient's hemolysis began at 0.40 and was complete at 0.24. Supernatant fluid of first tubes was yellow due to bilirubin; checked with serum in saline, plus water, gave the same color. (For analysis of the serum for lipids, see table 3.) Icteric index of 150; bilirubin, direct 15.9 mg. per cent; indirect 20.4 mg. per cent. Fasting blood sugar examination was 100 mg. per cent. The bromsulfalein liver function test, using 5 mg. per kilogram of body weight, showed over 50 per cent retention in one-half hour and 50 per cent retention in one hour. Blood sedimentation rate was 18 mm. in 20 minutes, 66 mm. in one hour, and 112 mm. in two hours by the Westergren method. Serology: Hinton, Wassermann and Kahn tests negative. Blood lipase: 0.48 c.c. of .05 normal potassium hydroxide per 1 c.c. of serum (lower limit value for lipase in serum of normal individuals). Prothrombin time, 35 seconds; normal control, 20 to 25 seconds.

Roentgen-ray Examinations: The following roentgenologic studies were done by Dr. Alice Ettinger: *Oral Graham test:* "Fourteen hours after double oral dye no distinct gall-bladder shadow can be recognized in the right half of the abdomen, which

can be considered to represent the gall-bladder. There is also no shadow after a fatty meal. Diagnosis: In the presence of jaundice, the lack of filling of the gall-bladder cannot be properly evaluated as to the presence of gall-bladder disease." *G. I. Series:* "Smooth passage of the barium through the esophagus. Slight herniation of the stomach mucosa above the diaphram. Normal relief; regular curvatures. The stomach is slightly displaced to the right by an enlarged spleen. Nothing unusual in the upper loops of the small intestines. Diagnosis: No x-ray evidence of varices or any pathological lesion of the stomach, duodenum, and upper loops of the small intestines." *X-ray of the long bones and of the skull:* "There is no x-ray evidence of any bone changes." *X-ray of the chest:* "Both diaphragms are smooth in outline with clear angles. The lung fields are free from infiltration. The heart is normal in size and shape." Diagnosis: "There is no x-ray evidence of a pathological lesion of the chest."

Hospital Course: During the seven-day hospital stay the patient had no particular complaints. Request for a sternal puncture and peritoneoscopy as well as the gynecological examination was refused.

Patient was seen ambulatorily on May 29, 1941. She complained only about the itching of the skin. She claimed she kept her diet free of animal cholesterol and fat. She did her housework and even went out dancing several times. Physical findings were unchanged since her hospital admission. Liver and spleen were enlarged. No attacks of pain or fever. No ascites. No edema of the legs. (For analysis of serum lipids, see table 3.) Bilirubin: direct 12; indirect 16.

The patient was uncooperative and did not appear for another examination. Dr. E. B. Medoff, Woonsocket, R. I., reported that Mrs. P. H. died February 1943 "a rather slow lingering death accompanied by numerous hemorrhages from the gums, mouth, rectum and frequent vomiting of blood. An autopsy was denied."

TABLE III

Lipid Analysis of the Serum of Mrs. P. H.
The serum was transparent and not milky

	April 28, 1941	May 29, 1941	Normal
Total cholesterol	1535 mg. %	1140 mg. %	150–260 mg. %
Free cholesterol	275 mg. %	320 mg. %	40–70 mg. %
Cholesterol present as esters	1260 mg. % (82% of total cholesterol)	910 mg. % (79% of total cholesterol)	70–75% of total cholesterol

Clinical Comment: Patient P. H. exhibited the most extensive involvement of the skin with xanthomatous lesions in our experience (figures 10, 11, 12, 13). Since she was uncooperative toward the end, the clinical and laboratory follow-up studies in the final two years of her life are incomplete. It is evident from the report of the attending physician that her death was caused by bleeding from esophageal varices due to progressing cirrhosis, which finally also resulted in portal obstruction. It is noteworthy that at the height of her disease, during the period of clinical observation, the cholesterol esters were neither diminished nor were signs of portal congestion like esophageal varices present. As in the case of T. P. the symptoms of portal obstruction occurred in the last phase of her illness, but these features have no relation to the early manifestations of the disease. In other words, the histological demonstration of severe cirrhosis in the end stages of a case of xanthomatous

biliary cirrhosis should not be taken as a sign that skin xanthomas and chronic obstructive jaundice are complications of the common type of portal cirrhosis; rather the reverse sequence of events seems to occur. For years the fibrotic changes are localized around the finest ramifications of the bile capillaries and junction ducts producing the characteristic histological picture of pericholangiolitic biliary cirrhosis. In the last phases, however, the symptoms of portal congestion may develop and lead to the fatal outcome.

Case 4. This case published by Eusterman and Montgomery [18] is included in this report because one of us (MacMahon) through the courtesy of S. Warren Hunter, Department of Pathology, University of Ohio, studied the histology of the liver. The complete case history is found in the original paper. The patient, a 48 year old female, noticed in 1940 a "rash" of wide distribution. This eruption consisted of recurrent pruritic lesions, some of which the patient described as having a central plug without pustulation. (This type of papulo-pustular eruption has been described by Thannhauser and Magendantz in similar cases.) Yellow tuberous xanthomas had persisted and progressed since December 1940. Two years previously the liver was found to be enlarged. Jaundice was first observed in October 1940, eight months prior to the patient's admission. She had lost 40 pounds. The family history was without significance. The patient had abused alcohol for 10 years. There was no history of biliary colic or acholic stools.

Physical examination disclosed the presence of icterus, anemia and generalized xanthoma. Yellow nodules, 1 to 3 mm. in diameter, were present on the buttocks, lower part of the back, upper part of the thigh, elbows and both cheeks. Nodules and infiltrated plaques were found on the extensor surfaces of the legs, Achilles tendon and eyelids. In addition there were yellowish infiltrations covering the creases of the palms as well as discrete nodules on both the palms and soles. The liver was firm, insensitive and not especially nodular. However, it was considerably enlarged, the lower border extending one inch above the umbilicus. The spleen could not be palpated, and there was no evidence of the presence of ascites then or subsequently. Although the feces were normal in color, biliuria, grade I, was present. (Death occurred about one year later in California in August 1942 as a result of a massive terminal gastrointestinal hemorrhage.)

Laboratory Findings: Serum bilirubin was 5 mg. per cent and the van den Bergh reaction was direct. The hippuric acid test was normal. The albumin-globulin ratio was 1.1 : 1. The prothrombin time was within normal limits.

TABLE IV

Values for Plasma Lipids mg. per 100 c.c.
G. B. Eusterman and H. Montgomery

	March 24/41	May 17/41	May 26/41	July 8/41	July 25/41	Sept. 12/41	Dec. 11/41	April 15/42
Total cholesterol	1320	1388	1388	1193	926	820	1155	352
Cholesterol present as esters		666	980	374	443	625		
Lecithin		2592	1668	1087	1800	1330	1000	555
Total fatty acids		2107	1669	808	2240	800	620	
Neutral fat*		Neg.	Neg.	Neg.	Neg.	Neg.		

* The values for neutral fat were not charted in the paper of Eusterman and Montgomery but calculated by us according to the formula of Thannhauser and Reinstein[47] by subtracting the sum of the fatty acids present as cholesterol esters and glycerol esters present in the lecithin from the figures tabulated for total fatty acids.

One of the characteristics of the syndrome of xanthomatous biliary cirrhosis, according to Thannhauser and Magendantz, is the transparency of the serum despite the accumulation of cholesterol and lecithin, a fact explained by the normal or mostly low neutral fat content of the serum. In Esterman and Montgomery's case excessive hypercholesteremia and hyperlecithemia were present, but low, in fact, negative values for neutral fat can be calculated from these figures. It may therefore be surmised that the serum of the patient was transparent and not creamy. The term hyperlipemia, as Thannhauser [27] pointed out, should be used to signify only the accumulation of neutral fat while hypercholesteremia and hyperlecithemia of an extremely high grade may occur without hyperlipemia. This phenomenon of an extremely high cholesterol and lecithin content of the serum together with a low value for neutral fat, considered as characteristic of xanthomatous biliary cirrhosis, was also observed in the above case.

Pathology. A block of liver tissue removed at the time of the autopsy was very kindly sent on to us for study. The picture was one of a very advanced cirrhosis and, except for two minute fields, there was no evidence of an active inflammatory process. Large communicating bands of fibrous tissue containing few collapsed and compressed minute bile ducts divided the liver into nodules and lobules. In some of these nodules the parenchyma was well preserved and healthy central veins were easily discernible. In others, there were only nodules of liver cells and sinuses. It is important to note that the nodules and lobules of liver tissue were free of intralobular fibrosis. The pathological changes were so far advanced and the inflammatory reaction had so nearly healed that it was hazardous to guess what this liver was like in its earliest stages. The fact that the fibrosis was centered in the portal areas, and that many lobules with their central veins were still preserved strongly suggested that we were dealing here with a type of biliary cirrhosis, but it was impossible to say in so late a lesion whether it began as a cholangiolitic or pericholangiolitic process. It is important to note that, as in the other cases, no xanthoma cells were found in any of the bile ducts.

Case 5. A 46 year old married, white female entered the Evans Memorial Hospital, Boston, on August 19, 1943. Her chief complaint was jaundice of 16 months' duration.

Past History: In childhood the patient had had scarlet fever and diphtheria. Subsequently she had always been well until the onset of her present illness. She had, however, always been thin, her best weight having been 108 pounds. There was no history of typhoid, exposure to toxic chemicals or alcohol ingestion. Except for mild and transient bouts of diarrhea, there had been no specific gastrointestinal disturbances.

Present Illness: In January 1942 the patient began to feel weak and run-down but had no localized symptoms. Her friends and physician told her that she was quite jaundiced. Subsequently her stools became light, her urine dark, and her skin itchy; a dragging sensation developed in the right upper quadrant.

Since she obtained no relief from a low-fat diet, her physician sent her to the Pondville Hospital and told her she might have a "growth." On June 8, 1942 an exploratory laparotomy revealed no obstruction in the extra-hepatic biliary tract. A biopsy of the liver was obtained. A retrograde cholangiogram made after the operation showed no evidence of biliary tract obstruction.

Following her discharge from the Pondville Hospital, the patient weighed 88 pounds. Many excoriations developed on her skin in May 1942, some becoming secondarily infected. The excoriations bled easily, and there were several episodes of

epistaxis. The jaundice remained about the same. Anorexia was quite prominent, but there were no other gastrointestinal symptoms.

In March 1943 yellow plaques appeared on the margins of both upper lids. Subsequently other plaques developed on the flexor folds of her hands and both arms as well as on the back, neck, shoulders, and axillae.

Since the patient failed to show any appreciable change and since the attending physician noted progressive enlargement of her liver, she was admitted to the Evans Memorial for further study. At the time of her first admission the jaundice had already lasted for 16 months. The skin xanthomas had developed about nine months previously.

Physical Examination: Revealed a well-developed, moderately emaciated, jaundiced woman appearing older than her stated age, sitting in bed and scratching. Skin, sclerae and buccal membranes were icteric. Numerous xanthomatous plaques were observed in the axillae, on the flexor surfaces of the arms and hands, and on the posterior surfaces of the thorax, and on the eyelids. Several of these were excoriated. The hair follicles over the extensor surfaces of the thighs showed papulo-pustular eruptions. There were no petechiae or spider angiomata. Pupils were reactive. Marked dental caries. One bleeding fungating nodule, 4 mm. in diameter, was noted below the left lower canine tooth. Thyroid was not enlarged. Lungs were clear and resonant. Heart was not enlarged. Rate 60; regular. Blood pressure 150/62. No peripheral sclerosis. Liver palpable four fingers below the right costal margin; firm, nodular and non-tender. Spleen not palpable—slight tenderness in right lower quadrant. Rectal examination revealed no hemorrhoids. Cervix uteri posterior; non-tender. Reflexes hyperactive. Weight 98 pounds.

Laboratory Data: Hinton negative. Urine: Color dark brown to dark yellow. Specific gravity ranged from 1.017 to 1.027. Bile 4 + on 13 occasions. Urobilinogen was frequently present as high as 1:64 dilution. Sediment was negative. Red blood count ranged from 4.5 to 2.85 million and hemoglobin from 13 to 10 grams. Prothrombin time on two occasions 90.9 per cent of normal and 100 per cent of normal, respectively. Clotting time 14 minutes and 30 seconds. Bleeding time 3 minutes and 30 seconds. Clotting time, repeated, 15 minutes, and bleeding time, repeated prior to discharge, 3 minutes and 15 seconds. White blood count on admission 9,500 with 70 per cent polymorphonuclears, 25 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophiles. White blood count varied between 6,000 and the admission count with differential essentially the same. Non-protein nitrogen 26 mg. per cent. Total protein on two occasions 7.65 grams per cent and 6.26 grams per cent. Albumin on two occasions 2.97 and 2.38 grams and globulin 4.68 and 3.88 grams with A.G. ratios of 0.63 and 0.61. Icterus indices: 75, 90, 80, 80, 80, 60, 75, 83 and 90. Calcium was 8 mg. per cent. Phosphorus 3.96 mg. per cent. Stools brown, formed and firm. Guaiac negative. Stools were negative for pathological intestinal bacteria on culture. Hippuric acid excreted 1.28 gm. in two hours. (Unable to void in one hour.) Alkaline phosphatase 23 King-Armstrong units. Van den Bergh, qualitative, direct positive; quantitative, 5.23 mg. per cent. (Cholesterol figures, table 5.) Duodenal drainage; A. bile, light yellow; B. bile, light yellow; no crystals or parasites; microscopic: white blood cells and mucus. Carotene and vitamin A in serum; carotene was 20 gamma per cent (normal 100 to 250 gamma per cent). Vitamin A could not be read because of excess and abnormal lipid content. Serum total lipid content (ether extraction) 3.96 gm. per cent. Lipid tolerance test (1 gram fat per kilogram per os), fasting 4.32 gm. per cent; 3 hours 4.43 grams per cent; 5 hours 4.22 grams per cent. Serum lipase 0.64 c.c. NaOH (Normal). *Serum showed no gross lipemia, being quite clear. Chylomicrons were markedly reduced in number.* Three days stool; daily fat intake of 50 grams; weight of stool wet 454 grams; dry 148.5 grams; stool fat 49.6 grams/three days. Alkaline phosphatase repeated was 21 King-Arm-

strong units. Van den Bergh—immediate, biphasic, quantitative 6.75 mg. per cent of bilirubin.

Roentgen-ray Examination: Skull—vault not remarkable. No localized areas of erosion or hyperostosis. Vessel markings normal in size and distribution. No abnormality of bone texture noted. Sella turcica normal in size and contour. Pelvis—no evidence of bone pathology. Femora—poorly defined osteolytic areas at the distal end of each femur, not typical of any particular disease; soft tissue mass at the pelvis, probably due to distended bladder. Roentgenogram of the chest showed no evidence of active pulmonary disease.

Clinical Course: Patient spent 36 days in the hospital. Temperature showed a constant wide swing although almost always within normal limits except for two or three times when it rose to 100°. Pulse was in conformance with temperature but averaged between 50 and 70 throughout the hospital course. Intake and output were not remarkable. Patient was up and around during her stay, complaining only of intense itching on various occasions. Calcium gluconate was administered, 10 c.c. of 10 per cent solution, with occasional relief from itching. On admission the patient weighed 94 pounds and on discharge weighed approximately 93 pounds. Blood pressure during course averaged about 120/74.

The patient was placed on a low-fat, low-cholesterol diet. She was later given 20 gm. of lecithin t.i.d., as well as vitamins A and B complex and vitamin D. One tablet of desoxycholic acid was also given t.i.d. The patient, however, was unable to take the lecithin adequately.

Follow-up Notes: The patient was put on a diet containing 50 gm. of fat with no animal fat allowed. She was advised to eat as many protein rich foods as possible. She was given three tablets of vitamin B complex daily, 45,000 units of vitamin A and 9,000 units of vitamin D daily, and 1 mg. of vitamin K twice a week. Through the kindness of Dr. Lester Dragstedt she was given at first 12 and subsequently 15 capsules of lipocaic daily.

The patient made some improvement on this regimen. Her weight reached 101 pounds as compared to 93 pounds at the time of discharge, and she felt much stronger. On the other hand, the size of her liver did not change appreciably. The skin xanthoma were also unchanged. The laboratory studies showed no clear-cut improvement in the serum carotene, vitamin A and bilirubin content.

Second Admission: Red blood cells 1,620,000; hemoglobin 6.2 gm.; white blood cells 15,050. Differential count normal. Hematosis 11 per cent. M.C.V. 73. M.C.V. 36. Clotting time 4½ minutes. Bleeding time 5¼ minutes. During the patient's hospital stay red cell count improved: 3,720,000 red blood cells; 11.0 grams hemoglobin. Stool showed four plus guaiac from fifth to ninth day, two plus on tenth day and zero to one plus thereafter. Total protein 5.25. Albumin 1.94. Globulin 3.31. A.G. ratio 0.59. Roentgen-ray for esophageal varices negative. Cephalin flocculation test ++++.

Third Admission: Patient was on a diet low in animal fat and containing vitamin B complex and vitamin K. Jaundice has not increased or decreased although pruritus has been less marked. Two weeks prior to her third admission she had an episode similar to the one which precipitated her second hospital admission—weakness, dizziness, and passage of black stools. Three hours prior to the present admission she had another spell of weakness and passing of tarry stools. After transfusions she recovered but stools remained positive for six days.

Laboratory Data: Red blood cells 2,980,000; hemoglobin 7.6. gm.: white blood cells 12,050. Total protein 4.3. Albumin 2.1. Globulin 2.2. Patient was discharged with hemoglobin 12.9 grams, white blood cells 7,800. Cephalin flocculation ++++. Cholesterol analysis, see table 5.

Fourth Admission: On the day of admission the patient vomited several times.

Vomitus was of a coffee ground color. Patient was confused and dyspneic. Dyspnea disappeared when she lay down.

Laboratory Data: Urine 3+ bile. Hematocrit ranged from 14 to 35 per cent. Hemoglobin ranged from 5 to 5.5 gm.; white blood cells from 26,900 to 6,700 with normal differential count. Non-protein nitrogen 43 mg. per cent. Total protein 5.23. Albumin 2.55. Globulin 2.91. A.G. ratio 1:1. Cephalin flocculation 4+. Stools: guaiac 4+ for five days. For cholesterols, see table 5.

Fifth Admission: One week prior to admission the patient passed dark blood per rectum and felt weak. One day prior to admission the patient vomited bright red blood and passed dark blood per rectum. She felt weak and developed a terrible thirst. Temperature 98.6°. Pulse 102. Respirations 20. Skin dusky green-yellow hue. Skin xanthomas did not change from the time of her previous admissions. Light colored plaques ranging from 2 mm. to 3 cm. in diameter. Heart: systolic murmur; blood pressure 94/35.

Laboratory Data: Urine bile 9+. B.S.R. 99. Hemoglobin 4.9 gm.; and after 10 blood transfusions 11.5 gm. Prothrombin time 44.2 seconds. Control 20 seconds. Total protein 3.98. Albumin 1.87. Globulin 1.61. Total protein increased finally to 6.25 gm. Non-protein nitrogen 43 mg. Blood sugar 99 mg. per cent. Cholesterol values, see table 5.

Sixth Admission: Since her discharge the patient has been followed by Dr. F. Ingelfinger in the Outpatient Department of the Evans Memorial Hospital. For about six months she has had a warty "horn-like" papilloma at the inner canthus of the right eye. Four days prior to her admission following a minor trauma, she bled profusely and has continued to bleed intermittently despite ligation by her local physician. The patient has also noticed occasional bleeding from the gums. Itching was at times very intense. She followed only moderately well a fat-free diet.

Temperature 98.6°. Pulse 68. Small thin female, who appeared chronically ill but in no acute distress. Skin was of deep brownish-yellow color and contained numerous plain and tuberous xanthomas, particularly about the upper trunk and arms. Over the legs were papulo-pustular lesions. Mucous membranes of the mouth were deeply pigmented. Chest was clear to percussion and auscultation. Heart: Point of maximal impulse in the fifth interspace 7 cm. from the midsternal line and except for a grade 3 blowing systolic murmur was otherwise not remarkable. The liver edge was palpable below the level of the iliac crest and in the epigastrium. The liver was smooth and not tender.

Laboratory Data: Urine 4+ bilirubin and numerous tyrosin crystals. B.S.R. 108 per hour. Hemoglobin 10.8 gm. White blood cells 9,350. Fasting blood sugar 90 mg. per cent. Total protein 6.6. gm. Albumin 2.88 gm. Globulin 3.69 gm. Prothrombin time 22.4 seconds. (Control 19.8 sec.) Cephalin flocculation 4+. Thymol turbidity 36. Cholesterol and bilirubin, see table 5.

The lesion of the inner canthus of the eye was healed at the time of the patient's discharge. The patient was advised to stay on a high-protein, high-vitamin, high-carbohydrate, but low-fat diet. Arrangements were made to have her receive injections of vitamin K twice a week.

Pathology. A laparotomy * was done at the Pondville Hospital in June of 1942. Exploration revealed no extra-hepatic biliary obstruction.

Microscopic Examination: This was an unusually satisfactory section and included approximately 50 lobules. The section was well cut and beautifully stained. There were four serial sections on the one slide, affording an opportunity to follow a lesion from section to section.

* We are indebted to Dr. Gerald C. Leary, Resident Pathologist at the Pondville Hospital, for permission to study a section of liver and lymph node obtained by biopsy at the time of operation.

TABLE V
Case 5

	July 13, 1943	July 25, 1943	Aug. 19, 1943	Aug. 25, 1943	Aug. 2, 1944	Sept. 21, 1944, after Bleeding	Oct. 11, 1944	Dec. 14, 1944	Sept. 29, 1946	Oct. 3, 1946	Apr. 17, 1947	May 22, 1947
Total cholesterol	545 mg.%	600 mg.%	545 mg.%	600 mg.%	545 mg.%	375 mg.%	700 mg.%	500 mg.%	310 mg.%	226 mg.%	200 mg.%	275 mg.%
Cholesterol present as esters	220 (40% of tot. chol.)	220 (30% of tot. chol.)	220 (40% of tot. chol.)	220 (30% of tot. chol.)	200 (36% of tot. chol.)	200 (53% of tot. chol.)	333 (47% of tot. chol.)	379 (70% of tot. chol.)	250 (78% of tot. chol.)	160 (75% of tot. chol.)	95 (45% of tot. chol.)	92 (33% of tot. chol.)
Total bilirubin	5.2	6.7			7.8	1.5		28.6	11.52		43.1	
								12.3 dir. 16.3 ind.	4.08 dir. 7.44 ind.		18.6 dir. 24.5 ind.	
Alkaline phosphatase	23U	21U			17	24		45				
Total phospholipids												290 mg.%
Saponifiable lipids												194 mg.%
Total fatty acids												667 mg.%
Neutral fat												387 mg.%

The most striking change was a chronic inflammatory reaction in each portal area (figure 14). There was marked bile stasis within the lobules and this was concentrated in the central zones. A third change was the focal accumulation of inflammatory cells in nests within the lobules, and a fourth change was a focal derangement of the trabecular pattern of liver cells within the lobule. In addition to these there

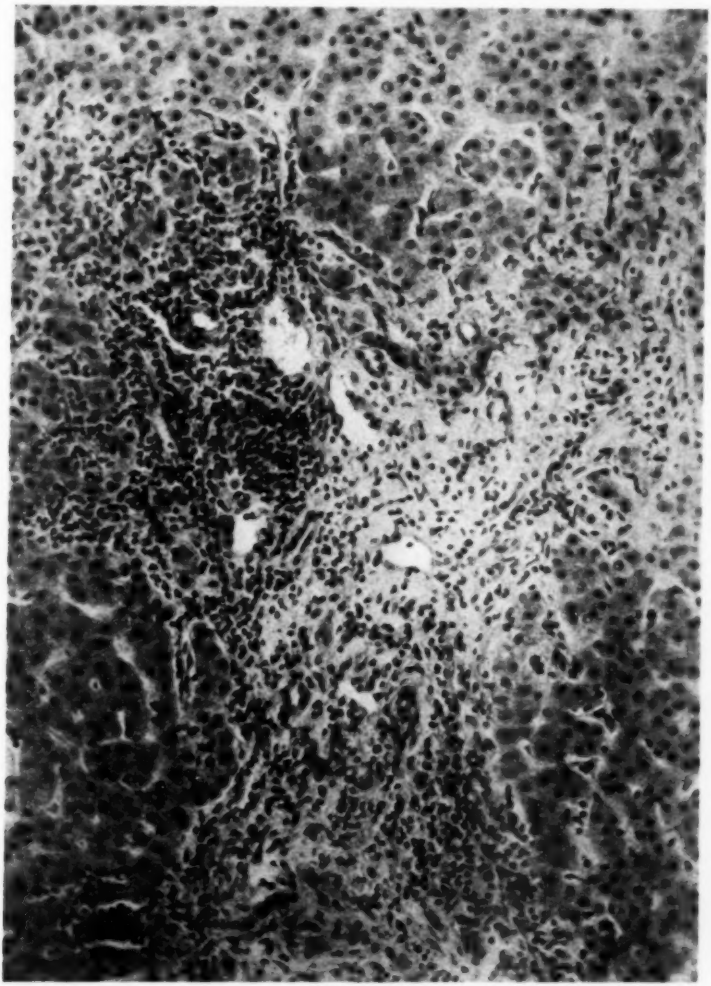


FIG. 14. Liver. This field was selected to show a widened portal area that is the site of a chronic inflammatory reaction. The exudate is dominated by lymphocytes and mononuclear cells. The inflammatory reaction seems to spill over into the adjacent lobule. Small bile ducts are inconspicuous.

was degeneration and necrosis of liver cells singly and in small clusters, but a very careful search failed to reveal a single mitotic figure in either liver cell or bile duct. The sinus endothelium was swollen. Some of the sinuses were dilated, others were compressed. The central veins for the most part were intact and free of abnormalities,

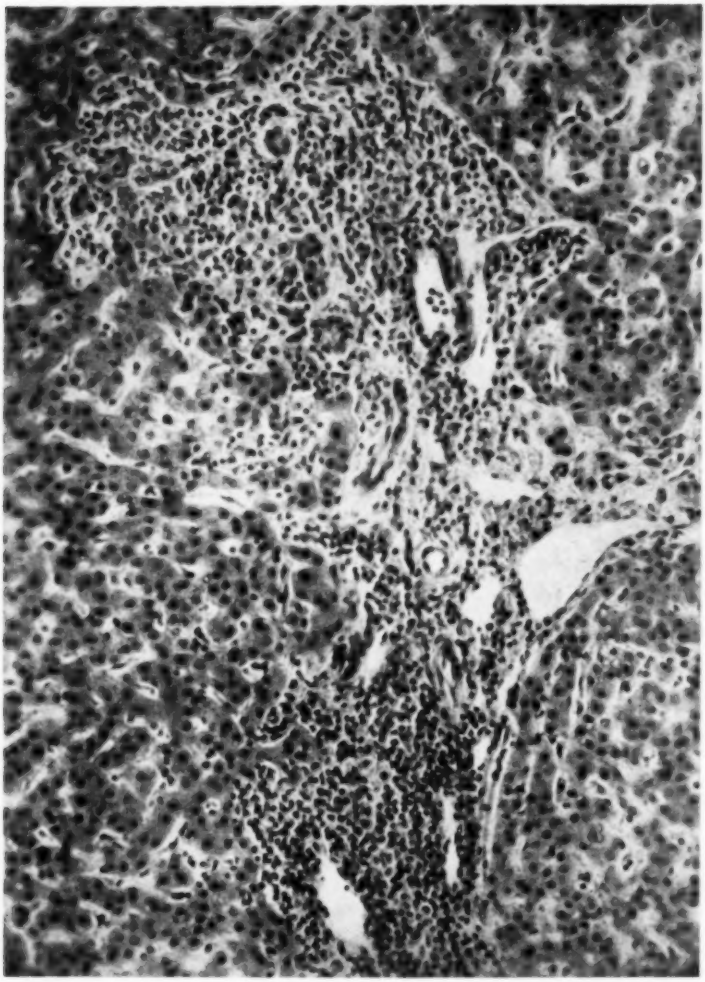


FIG. 15. Liver. This section was selected to show a portal area and the adjoining liver parenchyma. There is a very rich cellular exudate throughout the interstitial tissue. The granulation tissue almost hidden by this cellular exudate, reaches out into the adjoining lobules. Small bile ducts are empty and inconspicuous.

but occasionally a few lymphocytes were clustered in this area. This was particularly true when a band of inflammatory granulation tissue extended deeply into the substance of a lobule.

The oldest and most conspicuous change lay in the portal areas. These zones of connective tissue were larger, broader and in some places exerted an obvious compression effect on the adjacent liver parenchyma. In this biopsy specimen there were medium-sized and terminal portal areas allowing an opportunity to study the inflammatory reaction about the small and larger vessels. The inflammatory reaction was the same in the small and larger portal areas, but it differed in extent from one area to another. The reaction was confined to the interstitial tissue, though there were changes in bile ducts, veins, lymphatics and arteries. This reaction was dominated by a cellular infiltration and by a moderate proliferation of fibroblasts (figure 15). Lymphocytes, plasma cells and mononuclear cells were most numerous. In addition, there were polymorphonuclear leukocytes and a slight scattering of eosinophiles. In one field there was a very well formed lymph follicle. There was nothing specific about the inflammatory reaction and there were no xanthoma cells. The reaction, though diffuse in the portal areas, was most closely associated with the small and terminal bile ducts. No leukocytes were found within these ducts. The reaction extended to the outer margin of the portal area and spread in coarse and narrow extensions into the peripheral zones of the lobules. It blocked sinuses and isolated nests of liver cells.

This extension into the lobule was confined to the outer zones of the lobule, but occasionally, where lobule and central vein were close, it spread from one to the other. Mitoses were found in histiocytes, plasma cells and fibroblasts, but no mitoses were found in bile ducts or liver cells.

The bile ducts were of particular interest; all, large and small, were empty. The large ones were collapsed and the epithelium seemed hyperplastic and almost papillary (figure 16). At no point was the epithelial lining of the larger ducts interrupted. The medium sized ducts and the very small ducts were difficult to find. Those that were visible were intact and empty. Compressed liver cells and junction ducts, which are composed of modified liver cells, were very conspicuous. They turned and twisted and lay embedded in inflammatory granulation tissue. These compressed, twisted and branching ducts suggested at first glance a great increase in small bile ducts. The cells of the junction ducts often showed degeneration, necrosis and leukocytic infiltration. Some of these cells were deeply pigmented with bile. These junction ducts appear to have suffered the greatest injury. None of these cells showed fat vacuoles or hyaline degeneration.

The intralobular bile canaliculi showed the changes of long-standing biliary obstruction. Casts were found throughout the lobules. Some were obviously old and were lamellated (figure 17). There was a very definite intralobular bile stasis. The greatest concentration of bile was in the center of the lobule and in areas adjacent to these bile casts liver cells had undergone degeneration and necrosis.

In summing up the findings in this case, it seems important to point out that the inflammatory reaction was centered in the interstitial connective tissue and that the changes within the lobules were secondary to this inflammatory reaction in the portal area. Because of the location of the lesion, it seems reasonable to consider it as a form of chronic pericholangiolitis, and because there is already beginning cirrhosis, the diagnosis of pericholangiolitic biliary cirrhosis seems acceptable.

A section of lymph node, taken at the time of biopsy, showed three interesting changes. (1) There was a hyperplasia, swelling and accumulation of large mononuclear cells in dilated sinuses. The cytoplasm of these cells was clear and vacuolated, suggesting fat storage. (2) Many of the endothelial cells contained clumps of bile pigment. This clearly showed the effects of an intra-hepatic bile stasis and the extra-

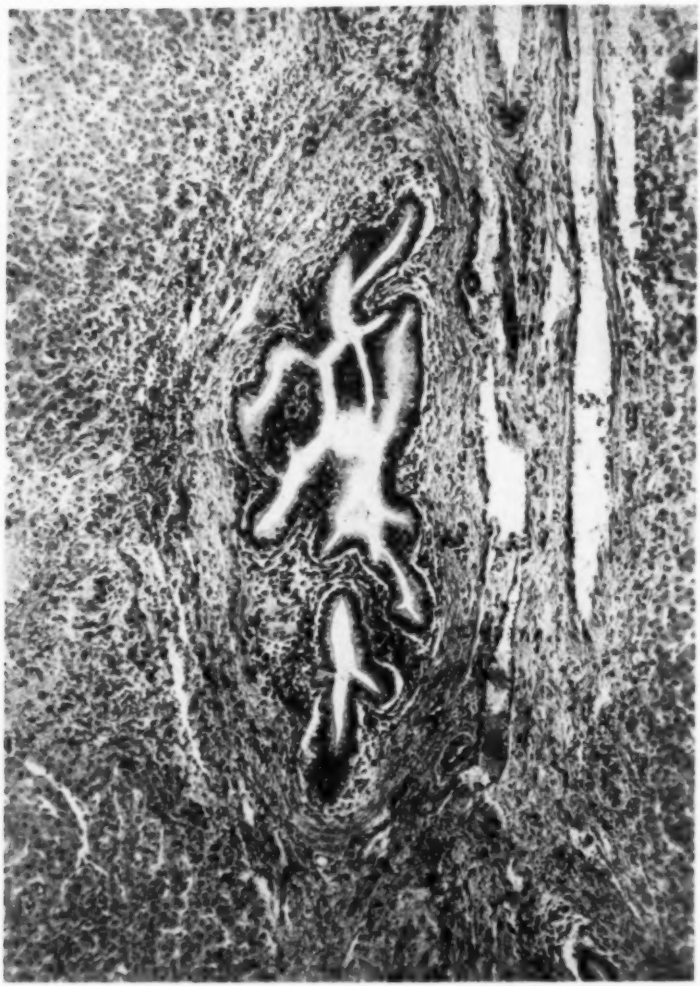


FIG. 16. Liver. This field was selected to show one of the larger bile ducts found in the biopsy specimen. The lumen is empty, the epithelium is well preserved and hyperplastic. The surrounding interstitial tissue is the seat of a chronic inflammatory reaction. No bile and no leukocytes are visible within the lumen.

vasation of bile from the liver into the lymphatics. (3) There were areas of necrosis, calcification and foreign-body giant cell reaction. A fourth finding, though much less significant, was a light eosinophilia throughout the section. In passing, it is interesting to recall that all of these findings in the lymph node may be seen in lymph nodes in cases of simple uncomplicated extra-hepatic bile stasis.

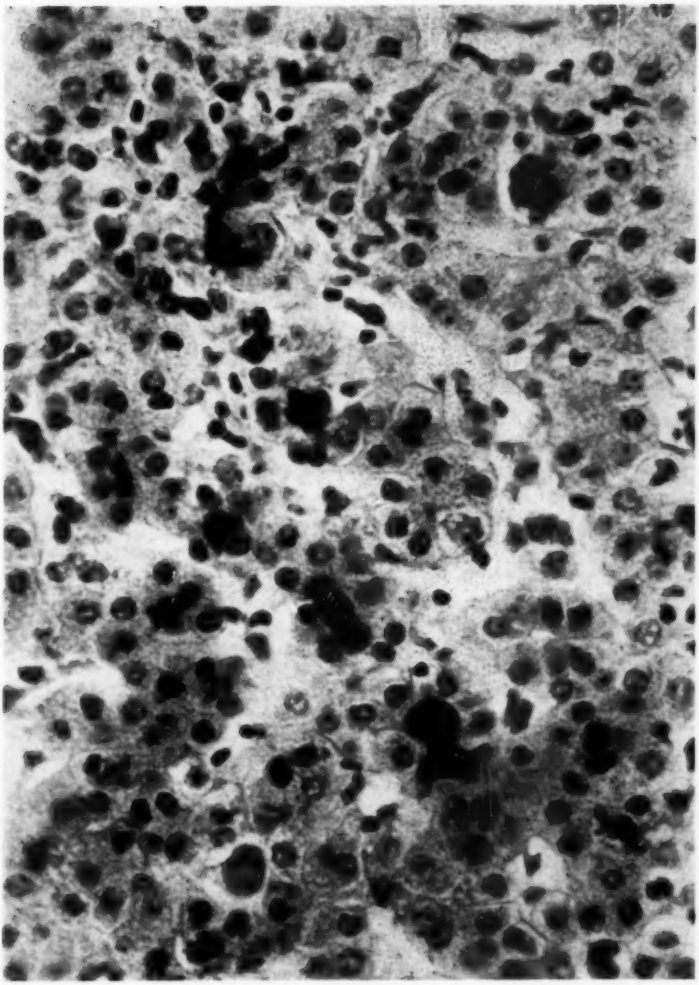


FIG. 17. Liver. This section was selected to show intralobular bile stasis. The bile canaliculi are distended with large deeply stained irregular and sometimes lamellated casts. Bordering liver cells show regressive changes and histiocytic infiltration.

Clinical Comment: In addition to the numerous tuberous and plain xanthomas patient 5 exhibited eruptive maculo-pustular lesions. This type of eruptive lesion, formerly described by Thannhauser and Magendantz, is not as these authors believed pathognomonic for xanthomatous biliary cir-

rhosis since one of us has observed meanwhile identical eruptions, which appear and disappear intermittently and itch intensively, in rare cases of chronic infectious hepatitis. In contrast to xanthomatous biliary cirrhosis, skin xanthomas are not known to appear in chronic infectious hepatitis notwithstanding the fact that in these cases cholesterol, but not lecithin, is moderately increased in the serum.

Patient 5 did not show comparatively high cholesterol values. The cholesterols present as esters were already diminished one and one-half years after the onset of the disease; other cases observed maintained a normal proportion of total cholesterol to cholesterol present as esters for a long time. This case deviated from the pattern of cholesterol accumulation observed in other cases of this disorder. The chemical findings alone would not be sufficient to establish the clinical diagnosis beyond doubt if the histological findings of pericholangiolitic biliary cirrhosis in the biopsy at the beginning of the disease did not suggest the diagnosis of xanthomatous biliary cirrhosis.

Case 6. A 43 year old farmer's wife was admitted by Dr. W. C. Burrage to the Joseph H. Pratt Diagnostic Hospital on April 16, 1947.

Present Illness: In January 1946 the patient visited her physician because of nose bleeds, enlarged abdomen, light-colored fetid stools and much flatus. Her doctor informed her that she was jaundiced and her liver was enlarged. He gave her bile salts and vitamins and also placed her on a high-calorie, high-protein, high-carbohydrate and fat-free diet. One month later she complained of pruritus. She also experienced a pain in the right chest region with a fever of 104° F. Sulfadiazine was prescribed, and the temperature rapidly returned to normal. The patient remained in bed for approximately six weeks and was then referred to a specialist in Halifax. There a chest film was made, an upper gastrointestinal series was done, and her stools and blood examined. Her hemoglobin was normal. Her liver was still enlarged. Everything else was normal. The patient continued a fairly normal existence, getting adequate rest and subsisting on the regimen outlined by her physician. However, she slowly and gradually went off the diet. The pruritus became more intense. The physician increased her bile salts. As no improvement was noted, the patient was referred to Dr. Burrage of Maine, who recognized the nature of her disease and advised her to enter our hospital.

It was noted on admission that the lesions on her body, first noted by the patient's sister on September 1, 1946, had steadily increased in number. Almost every crease of her body showed hard, raised yellow nodules of varying sizes. Nodular xanthomas were seen on the hands, elbows, eyes, and both lower extremities as well as the trunk and back. Eruptive maculo-pustular lesions with a red base and a depressed head were also visible on the extremities. The true yellow xanthomas elsewhere over the body looked different and were not inflamed. The hands had always been dry. The pruritus, continuous since February, was possibly more intense. The bile salts had seemed to darken the stools, which were more brown than yellow. The really light stools observed approximately one month prior to admission, seemed to occur with excessive fat indulgence. The stools were bulky and well formed, and the odor was lessening. She had never noticed black or bloody stools. From the beginning of her illness the urine had been dark—a dark amber color. At times the odor was strong. She seldom had nose bleeds recently nor bleeding from any of the orifices. Occasionally her gums bled after she brushed her teeth. The patient menstruated last, one year before admission at the onset of her present illness. Her jaundice had varied in intensity. At times she had been quite yellow, at other times considerably

clearer of jaundice but she was never completely free of it. The patient had lost her voice two weeks ago. This began with a cold, and throat irritation. She had noticed a change in her voice since the fall of 1946 and could not sing as well as previously.

Family History: Mother is living and well at the age of 73. Her father drowned at the age of 30. Three sisters are all well. No family history of cancer, tuberculosis, kidney disease, heart disease, hypertension, nervous disease, convulsions or diabetes. No family history of similar lesions or allergy.

Past History: The patient had the usual childhood diseases. She had scarlet fever when she was approximately 20 years of age. No major operations or serious illnesses.

System Review: No headaches, vertigo, syncope, blurring, diplopia, scotomas, tinnitus or otorrhea; epistaxis has been mentioned. No dysphagia. No cough or chest pain. The patient stated that she perspired profusely, may have had hot "flashes." No hemoptysis, ankle edema, shortness of breath or palpitations. Appetite enormous; she stated that she could not get enough to eat. Her weight had been stationary. No nausea, vomiting or constipation. Since the onset of her present illness she has had more frequent bowel movements, now numbering two to four a day; in contrast to two bowel movements formerly. She has had nocturia, three or four voidings. Previously there had been nocturia once. There is no burning, dysuria or hematuria.

Habits: The patient does not smoke or drink. At the present time she is subsisting on a high-calorie, high-protein, high-carbohydrate, low-fat diet. She takes bile salts, iron and vitamins. She has also been given "biotol," and amino acid preparations.

Social History: She was born in New Brunswick, Canada, and came to this country at 18 years of age. She trained as a nurse at the Poughkeepsie Hospital. She married at the age of 37. Her husband is seven years her senior. They have two children. Her husband and children are well.

Physical Examination: Temperature 99.4°. Pulse 82. Respirations 18. Height 5′ 3″. Weight 127½ pounds. Blood pressure is 120/70 in the recumbent position. The patient is a well-developed middle-aged woman in no acute physical distress. She is pleasant, coöperative and intelligent. She speaks in a whisper because she is hoarse. The skin is dark brown and peppered with xanthomas which are elevated, yellow and hard and which vary in size considerably. Xanthomas are present practically all over the body, the neck, chest, back, arms, hands, and lower extremities. There are also maculopapular lesions on the lower extremities which are different from the yellow xanthomas. There is cracking about the creases of the hands, which are hard and dry and practically covered with xanthomas. Hard yellow elevated nodular lesions also appear over the dorsum of the hands and seem to be localized over the joints. Both elbow regions are involved, and lesions are found in the antecubital fossae and over the extensor joint surface. Both axillae exhibit white smooth hard lesions. The back is peppered with lesions, numerous areas of dark pigmentation unassociated with whitish discoloration are present. There is a chamois-like color to the skin around both eyes. The face is symmetrical. No sinus or mastoid tenderness. No exostoses. The auditory acuity is good. The tympanic membranes are intact. The pupils are round and equal, react briskly to light and accommodation. The extraocular movements are normal. There is no nystagmus, blepharitis, conjunctivitis, exophthalmos or enophthalmos. The ophthalmoscopic examination reveals well-defined discs with no retinal abnormalities, no hemorrhages or exudates. Nose: No septal deflection, rhinitis, perforation or polyps. *Oral Cavity:* No cheilosis. The teeth are in good repair. The tongue is not coated; it projects in the midline. The papillae are prominent. No stomatitis, gingivitis, glossitis or pharyngitis. There are no lesions similar to those observed over the body. *Larynx:* The patient has been hoarse for three months. The vocal cords are thickened. No definite xanthoma could be seen on

the infiltrated cords. *Neck:* No rigidity, tracheal deviation, thyroid enlargement or cervical adenopathy. The chest is symmetrical. The breasts are small, free of masses. No erosion of the nipples. There are small insignificant nodes in both axillae. The lungs, except for the right base, are clear to auscultation and percussion. The diaphragmatic excursions are good. The heart is normal in size and position; the rate is normal; the rhythm regular. There is a Grade I to II systolic murmur heard over the entire precordium. The abdomen is distended and asymmetrical. There seems to be a definite fullness in the right side of the abdomen and bulging in the right flank. On palpation one can feel a tremendously enlarged smooth liver that fills the entire abdomen except for the left flank. The spleen can be definitely felt and palpated two fingers below the costal margin. No inguinal hernia or adenopathy. The extremities are symmetrical. The lesions present over both lower extremities have been mentioned. No peripheral edema. The dorsalis pedis pulsations are good. Skeletal system: The spine exhibits the normal curvatures. No tenderness elicited on percussion along the spine. The joints are all freely movable. Neurological examination: The muscle tone and strength good. No atrophy, paralysis, fibrillation or tremor. Coördination tests well performed. Sensations intact. Reflexes: Active and equal bilaterally. No pathological reflexes were elicited. Pelvic examination: External genitalia normal. There is a Grade III to IV cystocele. Marital introitus. The cervix is normal in position. There is a polyp protruding from the cervical os. The uterus and adnexa were not palpated. Rectal examination: Sphincter tone good. No hemorrhoids or masses outlined. The stool was brown. There is no fluid in the abdomen. No shifting dullness.

Laboratory Data: Urine: Reaction alkaline; sugar 0; albumin 0; specific gravity, 1.023; on microscopic examination rare red blood cells and leukocytes; few squamous epithelial cell and very rare mucous threads; bile +; urobilinogen ++, urobilin ++++, Wallace and Diamond test, 1:80.

Blood: Hemoglobin 11.5 gm.; red blood cells 3.57 millions; color index 1.02; white blood cells 9,450; polymorphonuclears 69 per cent; band forms 5 per cent; lymphocytes 20 per cent; monocytes 6 per cent. Blood smear: Occasional target cell. Few macrocytes. Rare polychromatophilia. No rouleaux. Platelets normal in number.

Blood chemistry: F.B.S. 87 mg. per cent; total serum proteins 8.0 mg. per cent; albumin 3.7 mg. per cent; globulin 4.3 mg. per cent. Total bilirubin 9.0 mg. per cent; direct 7.1; indirect 1.9.

TABLE VI

Lipid Findings in Serum of Case 6

	April 14, 1947	April 17, 1947	June 2, 1947	Sept. 1947
Serum: appearance	yellow-green clear	yellow-green clear	yellow-green clear	
Cholesterol—total	920	962	850	616
Cholesterol—free	830	915	750	448
Cholesterol—esters	90 (9.8% of total chol.)	47 (4.9% of total chol.)	100 (11.8% of total chol.)	168 (27% of total chol.)
Phospholipid total	1750	1325	1750	
Saponifiable lipids: (Lecithin and cephalin)		1071	1200	
Total fatty acids	1540	1280	1700	
Neutral fat	235	230	0	
Bilirubin total	9		6.9	
Total protein	8			
Albumin	3.7			
Globulin	4.3			

Serology: Blood sedimentation rate, 20 minutes 28; 1 hour 81. Prothrombin time 26 seconds. Control, 24 seconds.

Pathology. The specimens consisted of two small fragments of liver tissue, each approximately 0.4 by 0.3 by 0.2 cm. On each, there was a small but smooth area of capsular surface. The tissue was heavily bile-stained, finely nodular, and firm. It cut with resistance and had a coarse texture.

Microscopic Examination: Five sections were studied immediately on this viable, fresh unfrozen and unfixed tissue. Each showed a lengthening and widening of the portal areas with an increase in interstitial fibrous tissue, and a very rich lymphocytic infiltration. The central veins and the lobular pattern for the most part, were well preserved. By elongation and fusion with one another, the enlarged portal areas had already formed a well advanced perilobular form of cirrhosis. No bile was seen in these widened portal areas. This stood out in marked contrast to the extreme degree of bile retention within the lobules. All sections were studied with a polarizing microscope and all failed to reveal any doubly refractile fat. No xanthoma cells were found in any part of the sections. The portal veins and arteries in the portal areas were inconspicuous. The terminal bile ducts were very difficult to find. There was no bile within any of the terminal bile ducts. While the portal areas and lobules were clearly demarcated from one another, it was possible to trace delicate icicle-like projections of fibrous tissue from the portal areas out between the liver cells of the peripheral zones of many of the lobules. A "rapid section diagnosis" made at the moment of biopsy was that of chronic pericholangiolitis with beginning pericholangiolitic biliary cirrhosis. There was no evidence of tumor, or signs of extrahepatic biliary obstruction, and there was no evidence of an active cholangitis. The degree of liver cell degeneration was very limited.

Later, when the paraffin sections were ready, a very careful histological study confirmed the earlier diagnosis. Many of the lobules were well preserved and many of the central veins remained unchanged in the centers of the lobules (figure 18), but in other areas central veins lay in close communication with widened portal areas (figure 19). There was considerable loss of liver cells from the peripheral zones of the lobules. The most striking finding was the presence of an unusually active chronic proliferative inflammatory reaction in the interstitial tissue of the portal areas. There were many polymorphonuclear leukocytes throughout the inflammatory granulation tissue. The junction ducts were increased and numerous. They lay embedded in inflammatory granulation tissue. They branched, twisted and turned, but could be readily followed from the lobules into the granulation tissue of the portal areas. There were very few recognizable terminal bile ducts or cholangioles. In the paraffin sections, bile casts were numerous in bile canaliculi and in dilated junction ducts, but no casts were visible in the terminal bile ducts. The inflammatory infiltration extended well out between the liver cells in the peripheral zones of the lobules and in this area the liver cells showed degeneration and necrosis.

The overall picture was one of a very active chronic interstitial hepatitis centered about the terminal bile ducts and junction ducts at the outer margins of the lobules. There was an increase in fibrous tissue, a widening and fusion of the portal areas, and a well advanced perilobular fibrosis. No xanthoma cells were found in any of the portal areas. The final diagnosis was chronic pericholangiolitic biliary cirrhosis.

This case shows the greatest destruction of liver tissue of any of the early biopsies and in some areas it is possible to find fields that are indistinguishable from those seen in subacute and chronic cases of infectious hepatitis (figures 20, 21, 22). The complete picture, however, was distinctly one of an inflammatory reaction concentrated in the portal areas.

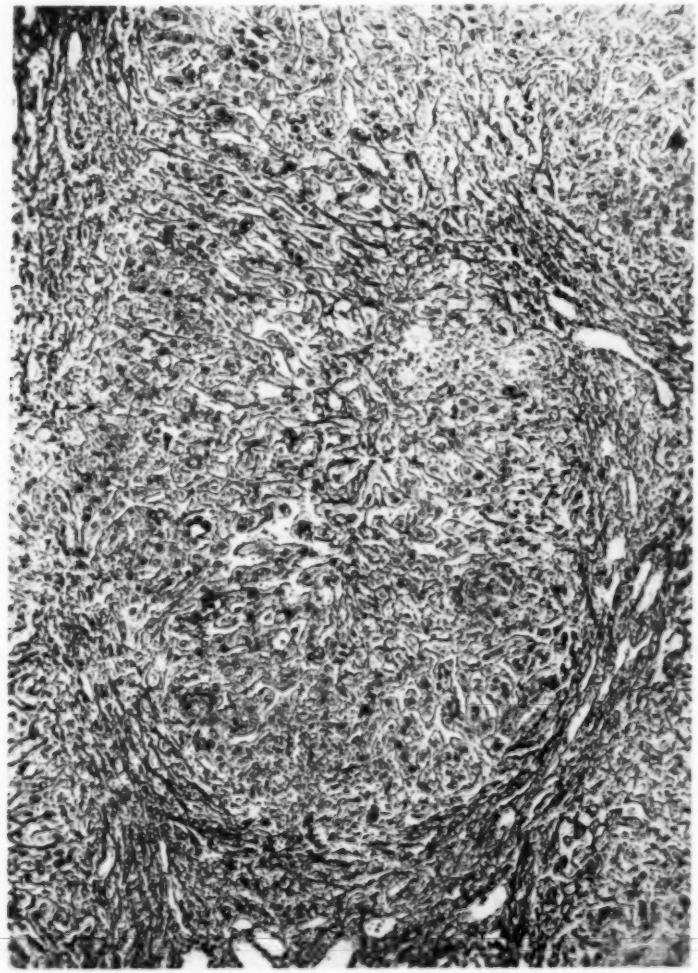


FIG. 18. Liver stained for reticulum. A solitary lobule occupies almost the entire field with the central vein in the middle. There is no increase of reticulum within the lobule although it is slightly concentrated in the central zone. In the peripheral zone there is not only a condensation, but an actual increase radiating out from the portal area.

Clinical Comment: This patient (Case 6) exhibited most extensive xanthomatous lesions, especially of the "plain" variety. Conspicuous not only on both eyelids and on the creases of the palm, these "plain" lesions were developed almost every place where the cutis is rather loosely attached to

the subcutaneous tissues and wrinkles in longitudinal folds such as around the neck, in the axilla, and on the folds of the buttocks. The patient also had itchy maculo-pustular eruptions on the trunk and especially on both legs. It should again be emphasized that these maculo-papular lesions are not the result of scratching.

The patient's liver was extremely large and almost filled the whole abdomen while the spleen extended only about one inch below the left costal margin. The liver, visible while a laparotomy for the biopsy was performed, revealed a fine granular surface with longitudinal scarring. Its color was reddish brown. Ascites was not present in the abdominal cavity.

The analysis of the serum lipids showed high values for lecithin (1071 mg. per cent) and total cholesterol (962 mg. per cent) but only 5 per cent of the total cholesterol was present as esters. These findings may be interpreted as indicative of severe damage of liver parenchyma. In this case, in contrast to other instances of acute damage of liver parenchyma, such as in acute yellow atrophy of the liver or in fulminant cases of acute infectious hepatitis, the drop in cholesterol esters (Estersturz [28]) did not occur together with low total cholesterols but on the contrary with very high cholesterol in the serum. This remarkable phenomenon may signify that increased cholesterol formation is not checked in xanthomatous biliary cirrhosis even when an intercurrent parenchymatous damage impairs the esterification of cholesterols. It is unlikely that retention alone causes this phenomenon of very high cholesterol and very low esters. The increased formation of cholesterol is, however, lessened when in the course of the disease the liver parenchyma is replaced by fibrotic tissue as seen in Case 1 and Case 2.

General Discussion

Age and Sex: The patients in the group of reported cases of xanthomatous biliary cirrhosis, have been between 30 and 50 years of age, with the exception of a seven year old girl described by Freda K. Herbert.[17] With the exception of Moxon's case,[2] the cases reported so far [16, 17, 18, 19, 20, 22] have been female patients.

In regard to reported male patients with hepatosplenomegaly, slight jaundice, melanotic pigmentation of the skin, increased total cholesterol and lecithin, and skin xanthoma, the question arises as to whether these cases should be classified under xanthomatous biliary cirrhosis. Cantarow and Bucher,[29] in a paper titled "Hemochromatosis," described a 45 year old man with a large liver and spleen and xanthoma on both eyelids, flexor and extensor surfaces of the elbows and on the creases of both palms. There were also a blue bronze pigmentation and slight jaundice but no glycosuria. (Serum cholesterols: total cholesterol 275 to 490 mg. per cent; cholesterol present as esters 114 to 333 mg. per cent; free cholesterol 33 to 157 mg. per cent.) The autopsy of the patient revealed hemochromatosis of the liver, most extensively in the pancreas and lymph nodes.

Eusterman and Montgomery [18] refer in Chart 1 Case 2 in their paper to a 42 year old male with large liver and spleen, xanthoma of the eyelids, slight jaundice, melanosis and glycosuria. (Serum lipids: total cholesterol 536 mg. per cent; lecithin 557 mg. per cent, total fatty acids 884 mg. per cent.)

One of us (Thannhauser) saw in consultation a 40 year old man with xanthomas on eyelids, elbows, buttocks and creases of the palms. His liver and spleen were considerably enlarged; he was slightly jaundiced and showed deep bronze pigmentation over the whole body but no glycosuria. (Serum lipids: total cholesterol 417 mg. per cent; cholesterol-ester 40 per cent of total cholesterol; total phospholipids 643 mg. per cent; lecithin 600 mg. per cent.)

It seems unlikely that these three male patients had xanthomatous biliary cirrhosis. The autopsy of the patient of Cantarow and Bucher revealed hemochromatosis of the liver, lymph glands and extensive hemosiderosis of the pancreas resulting in chronic pancreatitis. It seems probable that the two other deeply melanotic pigmented male patients also had hemochromatosis.

Why patients with hemochromatosis develop in rare instances skin xanthoma is a question that cannot be definitely answered. The following suggestions may be offered: 1. In the case of Cantarow and Bucher chronic hemosiderosis of the pancreas may have resulted in hyperlipemia and hypercholesteremia and secondary skin xanthoma. An increase of neutral fat in the serum would have to be expected, if hyperlipemia secondary to chronic pancreatitis was the cause of xanthoma formation in these cases. Unfortunately neutral fat had not been estimated in any of the three cases. 2. The hemosiderin deposits in the liver may have injured and obliterated the same areas of the finest bile capillaries as those which we have described as concerned with the underlying pathology of xanthomatous biliary cirrhosis. This second suggestion seems unlikely since neither the jaundice nor the hypercholesteremia nor the hyperlecithemia were as pronounced as in xanthomatous biliary cirrhosis. In the future a detailed analysis of the serum lipids, especially the presence or absence of hyperlipemia (increase of neutral fat) will clarify the etiology of skin xanthomas in such cases of hemochromatosis.

Concerning the sex incidence of xanthomatous biliary cirrhosis it has to be assumed from present evidence that this syndrome with its typical features has so far been observed only in females.

Heredity: In none of the cases reported was a familial occurrence revealed by the history. The group of "hypercholesteremic familial xanthomatosis," characterized by tuberous and plain xanthomas of the skin, tendon xanthoma and atheroma formation on the inner lining of the arteries, is a disorder which runs in families.[14, 15, 30, 31, 32] Thannhauser and Magendantz [14, 15] formerly believed that xanthomatous biliary cirrhosis also belonged to this group.

This opinion can no longer be maintained since in the meantime no familial incidence of xanthomatous biliary cirrhosis has been found in the cases described. It now is apparent that xanthomatous biliary cirrhosis is primarily a liver disease and a clinical entity by itself.

Clinical Features: The onset is insidious. The patients complain of itching of the skin, which is speedily followed by jaundice of the obstructive type, i.e. bilirubin giving the direct and indirect van den Bergh reaction is found in the serum. The jaundice remains until the fatal end of the disease. The grade of the jaundice does not vary much during the course of the disease and seems rather independent of the development of the skin xanthomas and of the fluctuation of the cholesterol and lecithin values in the serum. Fever or chills are not a feature of the disease. The development of fever is a sign of an intercurrent complication (see Case 1). The absence of fever probably explains in part why the patients feel relatively well during the course of the disease and are able to do their housework. The skin xanthomas may appear simultaneously with the jaundice or in most cases develop many months later. The tuberous deep yellow xanthomas are observed on the face, the elbows, the arms, fingers, buttocks and the distal parts of the lower extremities. Plain xanthomas appear on the eyelids, the creases of the hand and in rare instances also in places where the skin is loosely attached to the underlying tissue forming folds as in the axillary folds and in the folds of the skin of the buttocks. The localization of the skin xanthoma is different from that in the so-called "disseminata" type of xanthoma characteristic of "normocholesteremic xanthomatosis," as seen in Schüller-Christian's disease (lipid granulomatosis, eosinophilic xanthomatous granuloma). In this latter entirely different type of disease the xanthomas are light yellow or deep sepia brown, disseminated around the neck and the trunk and arranged in linear clusters in the axilla. The skin xanthomas in xanthomatous biliary cirrhosis persist during the entire course of the disease. The liver and spleen also remained enlarged. In some cases (Case 6) the liver extends in the midline over the umbilicus; in others it is only moderately enlarged. The surface of the liver is very firm but not nodular. The color, visible in early exploration is brownish-red or green, and the surface is smooth or slightly granular. Later stages reveal longitudinal scarring and larger granulation of the surface. Ascites is not a feature of the disease. Sometimes a peculiar maculo-pustular eruption, which appears and disappears intermittently, is seen all over the body, and especially on the trunk and the legs. First inspection gives the impression that these lesions are only the result of scratching but upon closer observation one sees the sunken-in head of the lesion mostly covered by a small crust. The eruption is inflammatory in nature and does not contain foam cells. Since similar eruptions occur in rare cases of chronic infectious hepatitis with chronic jaundice and moderately elevated cholesterols in the serum, this type of maculo-pustular eruption, even if most frequently observed in xanthomatous biliary cirrhosis, is not an exclusive feature of this disease.

Analysis of the serum lipids provides the most decisive findings for the diagnosis of xanthomatous biliary cirrhosis. The serum is transparent and not creamy throughout the disease. It contains normal or very low amounts of neutral fat despite its enormously increased content of cholesterols and lecithin. At the beginning the total cholesterol values of the serum may surpass 1500 mg. per cent. The cholesterol present as esters in the first year is normal, i.e. 70 to 75 per cent of the total cholesterol. The percentage of the esters may even be higher than these normal figures. After several years, the values for total cholesterol decrease but remain high; the percentage of the cholesterol present as esters becomes lower, and the free cholesterol is more prominent. The high values for lecithin decrease slowly with those for total cholesterol but are found even in the last stages. A tendency towards bleeding, such as is observed in other forms of chronic jaundice, is not marked. The prothrombin time, in the first years, is usually normal. In the final phase, however, bleeding from the gums, and vomiting of blood due to rupture of esophageal varices is observed. Profuse hemorrhage from esophageal varices is the most common terminal event. The development of portal congestion occurs, however, very late in the course of the disease. Roentgen-ray pictures of the esophagus during the development and the height of the disease do not show esophageal varices. At this stage other signs of portal congestion like ascites or spider veins are absent. Hepatic insufficiency resulting in hepatic coma was not observed in our cases. Liver function tests are not of great value for the diagnosis of xanthomatous biliary cirrhosis since the clinical symptomatology is typical in all cases, namely: (1) Skin xanthoma of the plain and tuberous variety. (2) Enlarged liver and spleen. (3) Obstructive type of jaundice of years' duration. (4) Extremely high values for total cholesterol as well as for lecithin. (5) The serum is transparent and not milky because of its normal or rather low content of neutral fat.

Pathology

Early Biopsies: In the portal areas there was a chronic proliferative and exudative inflammatory reaction, which was most concentrated about the junction ducts (canals of Hering) and terminal bile ducts (interlobular bile ducts or cholangioles) at the periphery of the lobules (figures 1, 2, 14, 15). The portal areas were larger, broader and longer than usual and often fused with one another to form rings of perilobular fibrosis (figure 18). Inflammatory granulation tissue extended into the periphery of the lobules. It blocked canaliculi, destroyed liver cells and collapsed many sinuses (figure 3).

The larger bile ducts were patent and empty. The small interlobular bile ducts were very difficult to find and in many of the portal areas there were none. The junction ducts which in a normal liver are so inconspicuous, were numerous, elongated, branching and tortuous. Some were dilated and filled with bile, others were collapsed and empty. None of the ducts con-

tained leukocytes, although several types of inflammatory cells including lymphocytes, plasma cells, histiocytes, neutrophiles and occasionally eosinophiles, richly infiltrated the surrounding granulation tissue.

The lobular pattern of the liver was well preserved and most central veins bore a normal relationship to the surrounding liver parenchyma. Large and

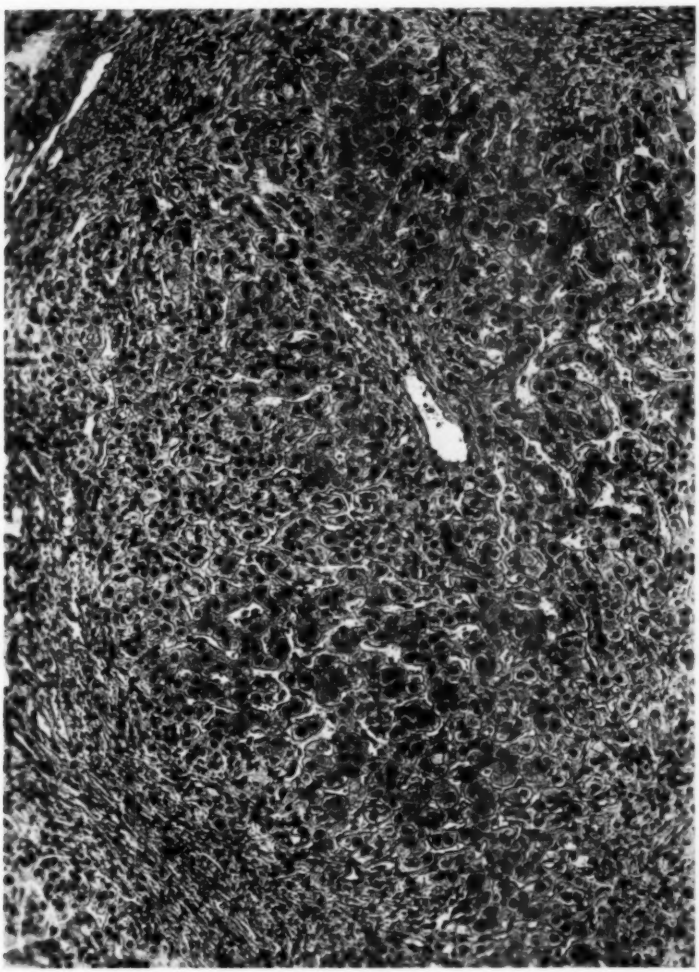


FIG. 19. Liver, showing an intact lobule with central vein clearly visible. The trabecular pattern is somewhat distorted and compressed and many small liver cells are mixed with those of normal size. A zone of inflammatory granulation tissue encircles the periphery of the lobule.

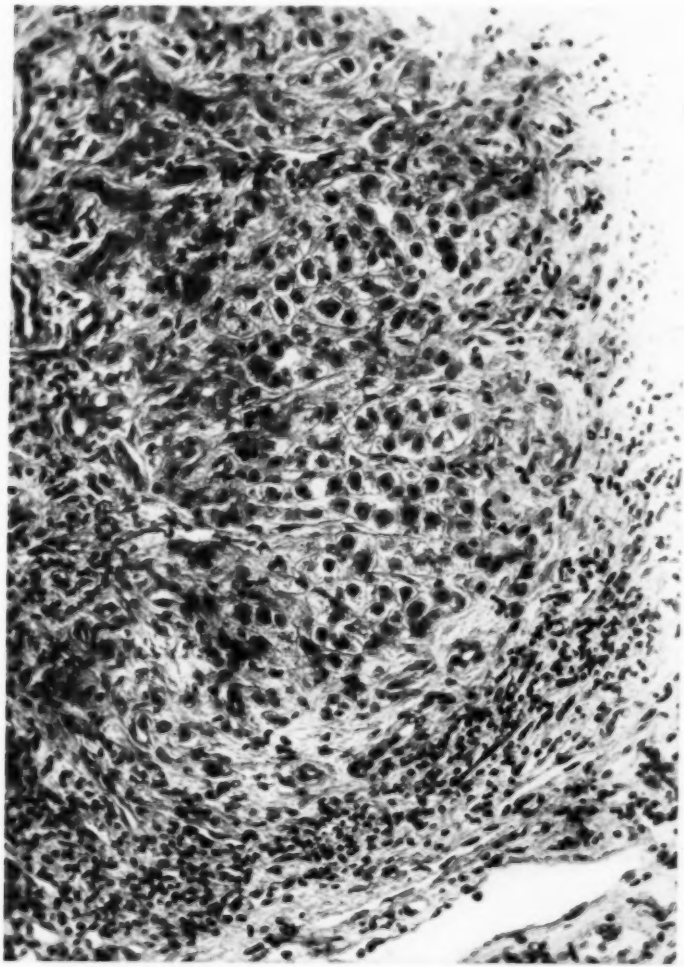


FIG. 20. Liver. A small nodule of compressed liver cells and sinuses. There is no central vein. This nodule of liver tissue is completely encircled by a widening zone of inflammatory granulation tissue radiating out from the peripheral zones of the lobules.

sometimes lamellated bile casts were fairly numerous within the lobules (figure 17). These distended the canaliculi and often damaged the bordering liver cells. For the most part the liver cells were healthy, few contained fat droplets and some lying in the field of inflammatory reaction about the portal areas showed degeneration and necrosis. There were few mitoses and the

presence of closely packed clusters of small cells near the periphery of the lobules suggested a moderate degree of liver cell regeneration (figures 4 and 19).

In one of the four biopsies the damage to the parenchyma was greater than in the others. In this biopsy, in contrast to the other, there were fields

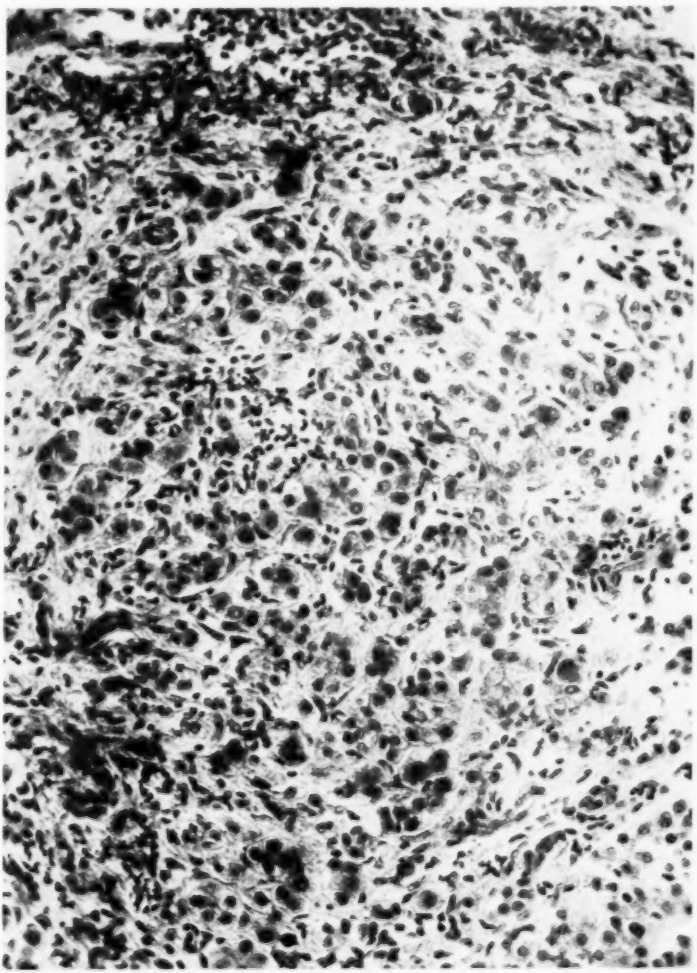


FIG. 21. Liver. This field was selected to show all that remains of a lobule of liver cells. There is an active inflammatory reaction at the periphery and extending along the sinuses between the liver cells. This was an unusual finding, but its resemblance to pictures seen in infectious hepatitis is at once obvious.

in which the inflammatory reaction had cut deeply into the centers of the lobules (figure 6). In this way central veins became linked with portal areas, and large and small islands of liver cells became isolated from the body of the parent lobules (figure 20). These islands, in turn, seemed to melt away to become replaced by inflammatory granulation tissue (figure 22). In one area an entire lobule had been destroyed and was now substituted by fibrous tissue.

The one fundamental histological finding common to all four biopsies was a chronic inflammatory reaction in the interstitial portal areas. It began as chronic pericholangiolitis and spread over into the peripheral zones of the adjacent lobules.

Autopsy Findings: To understand the development of the different types of cirrhosis it is necessary to know these types in all their stages. A study of this material afforded the opportunity to compare adequate sections from the livers of patients during life with sections obtained months and years later.

Grossly, the livers of the two patients who came to autopsy were large, firm, and cobbled. They weighed 2600 and 2800 grams respectively. On section the texture was coarse and bile-stained. There were no depositions of cholesterol in the mucosa of the gall-bladder or in any of the bile ducts. There were no concretions and finally, there was no suggestion of any type of extra-hepatic biliary obstruction.

The histology was much more complex and confusing than in the earlier biopsies. In a few areas the central veins, central zones and mid-zones were still recognizable, but for the most part, the normal lobular pattern in these late cases was severely distorted. Bands of fibrous tissue divided the parenchyma and not infrequently replaced whole lobules.

The parenchyma was composed of irregular cords of liver cells separated by edema fluid, dilated sinuses and fibrous tissue (figures 7 and 8). Here and there, the Kupffer cells were large, swollen and filled with lipoid, and nests of these occasionally distended the sinuses and compressed the adjacent trabeculae. There was much bile stasis with bile in the canaliculi, liver cells and sinuses.

The larger bile ducts were collapsed and empty. The terminal ducts were inconspicuous and embedded in fibrous tissue. In none of the ducts was there either an inflammatory exudate or any evidence of xanthomatosis.

The large size of the liver, the extensive fibrosis, the fragmentation of some lobules and the total loss of others, the nodules of regenerated liver tissue, the compression and interruption of liver cords by fibrous tissue, the patchy bile stasis, the intralobular lipoid deposition and finally, the presence of a still active chronic inflammatory reaction in portions of the interstitial tissue, all combined at this late stage to form a very confusing histological picture. If such a damaged liver were to be seen for the first time without an earlier biopsy, its pathogenesis would be difficult to unravel and its classi-

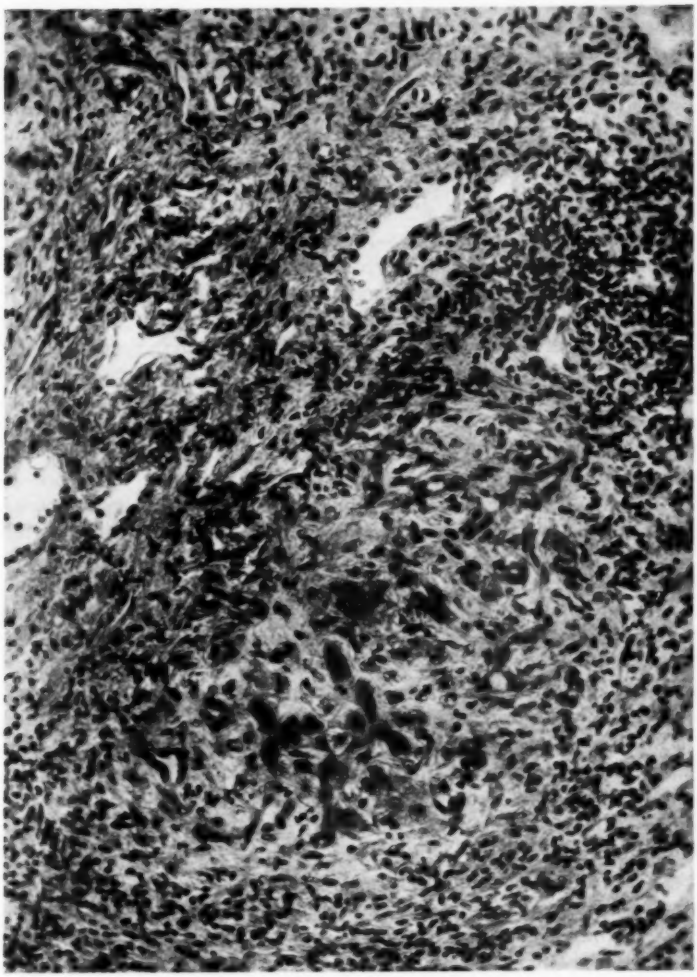


FIG. 22. Liver. This field was selected, and it is the only one of its kind in the entire section, to show how completely a lobule may be destroyed in this expanding zone of inflammatory granulation tissue. In the center of the field there are few moderately well preserved liver cells compressed together by this margin of granulation tissue. This particular field shows, perhaps, the most striking lesion in the biopsy, yet it is only fair to say that it was found only after long search and is not representative of the rest of the biopsy. All transition between this lesion and the inflammatory reaction in the portal areas could be identified.

fication would be uncertain. In this late stage it could easily be misinterpreted as an advanced stage of Laennec's cirrhosis.

Moxon [2] and Fagge [23] in 1873 reported the autopsy findings of two cases showing xanthoma of the skin with either atheromatous changes on the inner linings of the arteries or xanthoma formation on the linings of the bile ducts. Pye-Smith [3] in the same year described a third case of cutaneous xanthomatosis in which the patient showed cholelithiasis and dilatation of the extrahepatic biliary ducts. The liver of this patient showed changes suggesting a slight degree of interstitial fibrosis. Of this particular case Pye-Smith wrote: "The patches in the ducts looked just like atheroma in the artery with which condition, indeed, they corresponded histologically."

On this evidence, Thannhauser and Magendantz suggested that xanthoma formation of the bile ducts resulting in xanthomatous scar tissue might be the cause of the clinical syndrome which they had designated as xanthomatous biliary cirrhosis. It was their opinion that the development of the xanthoma of the skin as well as the xanthoma formation within the bile ducts, was the expression of a primary systemic disease characterized by an increased formation of cholesterol with hypercholesteremia (hypercholesteremic xanthomatosis). The xanthomatous involvement of the large bile ducts and their partial obstruction was thought to be the primary event which resulted later in this special type of biliary cirrhosis (xanthomatous biliary cirrhosis).

This opinion can no longer be maintained since our biopsies taken during the early stages as well as the autopsies years later of cases of xanthomatous biliary cirrhosis did not reveal the anticipated xanthomatous changes in the linings of the bile ducts. The biopsies in the early stages showed a proliferative and exudative inflammatory reaction about the smallest of the interlobular cholangioles and junction ducts extending into the periphery of the lobules. The autopsies showed cobbling of the liver, marked enlargement of the liver and advanced cirrhosis. At this late stage the initial and characteristic pericholangiolitic changes were difficult to see. When such a cirrhotic liver is seen without previous biopsy, an accurate diagnosis would be difficult and its pathogenesis would be uncertain. It is now believed on the basis of biopsies and autopsies of cases showing the clinical syndrome of xanthomatous biliary cirrhosis in the absence of any obstruction of the large ducts, that the histopathological findings in the liver justify the recognition of a special type of cirrhosis which may be designated anatomically as "pericholangiolitic biliary cirrhosis." [51]

Etiology: On the basis of the autopsy findings of Addison and Gull,[1] 1851, as well as Moxon,[2] 1873, and Pye-Smith,[3] 1873, Thannhauser and Magendantz [14] suggested that xanthoma formation of the larger bile ducts resulting in scar tissue may be the cause of the clinical syndrome described as xanthomatous biliary cirrhosis. These authors also believed at this time that xanthomatous biliary cirrhosis is a part of the syndrome of hypercholes-

teremic familial xanthomatosis, which is characterized by (1) tuberous and plain xanthoma of the skin, (2) tendon xanthoma and (3) atheroma formation of the inner lining of the blood vessels and (4) heredity. This etiological conception of the disease must be abandoned since neither surgical exploration, early biopsies of the liver nor autopsied cases reported in this paper revealed xanthomatous changes of the larger bile ducts which may have resulted in this type of biliary cirrhosis. Xanthoma formation of the lining of the bile ducts, as observed by the early authors, may occasionally occur as a rare side of xanthoma formation, but it is not the cause of this special type of biliary cirrhosis since it was not found by surgical exploration (Case 1) or at autopsy in the discussed cases.

One of us (MacMahon) found in the early biopsies a non-specific chronic inflammatory reaction centered around the smallest bile ducts and junction ducts in the portal areas, which is characteristic of the disease under discussion. There was blocking of the finest bile ducts and subsequent intralobular bile stasis. The larger bile ducts were patent and free. Thannhauser [24] has suggested an imbalance of cholesterol formation and excretion as the cause of xanthomatous biliary cirrhosis. At the outset of the disease the accumulation of cholesterol and lecithin in the serum might be caused by an increased formation of these substances in the liver as a result of a functional disturbance of the liver cells. Since liver biopsies have already revealed in the early stages of the disease anatomical changes around the finest bile capillaries, it seems doubtful whether an increased formation of cholesterols and lecithins ought to be assumed in addition to the histologically verified changes of the finest bile ducts, producing bile retention. In other words the question arises whether the extremely high content of the serum cholesterols and lecithin is due only to retention resulting from an impaired elimination or whether both processes, namely increased formation and retention of cholesterol and lecithin are responsible for the phenomenon resulting in the clinical syndrome of xanthomatous biliary cirrhosis. In the comment on the findings of Case 1, page 135, this problem is extensively discussed; therefore, only the main points are repeated. (1) The high cholesterol and lecithin levels of the serum are only moderately reduced after the beginning of diet treatment where the exogenous quota of animal cholesterol was almost completely restricted. This observation suggests that an excessive endogenous production of cholesterol and lecithin persisted during this period of restriction almost free of animal cholesterol intake. (2) The cholesterol concentration in the serum of Case 1 decreased markedly and was almost normal in the final period of the disease because an intercurrent tuberculous disease with miliary dissemination of tuberculous tissue in the liver caused the replacement of the liver parenchyma to a large extent. The obliteration of the finest bile capillaries producing the retention continued unchanged during the terminal phase, but not enough functioning liver tissue remained to maintain the formerly increased cholesterol formation.

(3) Complete obstruction of the common bile duct, as effected by occlusion by stone, carcinoma or fibrosis after a surgical accident usually does not result in an excessively high serum cholesterol and lecithin values (1550 mg. per cent and 2120 mg. per cent respectively) as in xanthomatous biliary cirrhosis (Cases 1, 2, 3, 4, 6). During the first stages of xanthomatous biliary cirrhosis at a time when such extremely high values in the serum were obtained as in Case 1, the liver biopsy showed obliteration of the small bile ducts only in some areas of the liver tissue. It therefore seems unlikely that the fibrotic obliteration of the cholangioles found in these areas at the beginning of the disease should result in a much greater cholesterol and lecithin retention than is true of complete obstruction of the common bile duct.[25] In complete obstruction of the common bile duct by stone, carcinoma or surgical obliteration, jaundice of severe grade, considerable increase of cholesterol and a slight increase of lecithin are observed, but skin xanthomas do rarely appear. The few instances of skin xanthoma after surgical obstruction of long duration [18] seem exceptional. In these rare cases the skin xanthomas disappeared with the restoration of the bile flow while in xanthomatous biliary cirrhosis they persist despite the fact that bile is constantly excreted in the intestines.

These considerations favor the suggestion of Thannhauser [24] that the marked accumulation of cholesterol and lecithin at the beginning of xanthomatous biliary cirrhosis is probably not only the result of a retention of bile but also the consequence of an imbalance of increased cholesterol and lecithin production and an inadequate excretion of these substances. The explanation of the finding of excessively high cholesterol and lecithin as the result of hyperproduction of cholesterol and lecithin in xanthomatous biliary cirrhosis remains a hypothesis. Such a hypothesis is, however, supported by the laboratory findings and by a comparison of this and other cases of xanthomatous biliary cirrhosis with other clinical syndromes where the obstruction and bile retention are complete and the only etiological factor. In the cases of complete obstruction the lecithin and cholesterol content of the serum is by far not as high as in xanthomatous biliary cirrhosis despite the fact that in xanthomatous biliary cirrhosis the bile passages are always patent.

Differential Diagnosis: The diagnosis of xanthomatous biliary cirrhosis should be ventured only if all five features of this disease are evident.

In the common varieties of biliary cirrhosis [48, 49, 50] neither skin xanthoma nor excessively high cholesterol and lecithin values of the serum are found. In infectious biliary cirrhosis, mostly due to an ascending infection of the biliary tract, periods of elevated temperature interchange with those of normal temperature; the temperature is normal in xanthomatous biliary cirrhosis. Differential diagnosis from acute and chronic infectious hepatitis is based on the absence in these conditions of widespread xanthomatous lesions of the skin and the abnormal lipid analysis of the serum. Xanthomas of the skin appear in xanthomatous biliary cirrhosis early in the disease together with excessively high total cholesterol and lecithin values in the serum. The per-

centage of cholesterol present as esters is high in the first years of xanthomatous biliary cirrhosis, 70 to 80 per cent. In the acute stage of severe hepatitis, however, the total cholesterol in the serum is never much elevated. The percentage of cholesterol present as esters is diminished in severe cases. The lecithin values in the serum do not rise markedly. The hepatosplenomegaly becomes more evident in the chronic stage of infectious hepatitis, but the serum analysis for lipids does not show a substantial increase of cholesterol. In most of the cases of chronic hepatitis the total cholesterol has a tendency to decrease, and the proportion present as esters remains or becomes low. The incidence of skin xanthomas in acute and chronic hepatitis is not mentioned, although the disease occurred in epidemics during the war. Only in one case observed by Watson and Hoffbauer [23] (case 7) did a male patient show xanthelasma of the eyelid. It was not stated, however, whether the isolated xanthoma had already been present before the hepatitis developed.

An eruptive type of xanthomas distributed over all parts of the body may occur together with hepatosplenomegaly as a consequence of various types of hyperlipemia. The hyperlipemia, i.e., the outstanding increase of neutral fat (10 to 60 times of normal) in these cases causes a milky or creamy non-transparent serum, readily recognized with the naked eye. Jaundice, despite the presence of hepatosplenomegaly in the hyperlipemic syndromes, is not observed. The following syndromes belong in this group of primary hyperlipemia with secondary skin xanthomas: (1) Idiopathic hereditary hyperlipemia [34, 35, 36, 37]; (2) Idiopathic non-hereditary hyperlipemia with and without slight glycosuria.[46] This group includes cases of primary hyperlipemia occurring together with hepatosplenomegaly as described by Buerger and Grütz.[38] (3) Secondary (transport) hyperlipemia as observed in severe untreated diabetes or in chronic pancreatitis [39, 40, 41] or in glycogen storage disease.[42, 43, 44] In all these syndromes of primary or secondary hyperlipemia with and without hepatosplenomegaly, the "creamy" hyperlipemic serum and the absence of jaundice immediately exclude a diagnosis of xanthomatous biliary cirrhosis.

Increase of skin xanthoma, chronic jaundice of slight grade, hepatosplenomegaly and considerable increase of cholesterol and moderate increase of lecithin have been described in the aforementioned rare cases of hemochromatosis. It must be admitted that the differential diagnosis of these cases from xanthomatous biliary cirrhosis may cause some difficulty since patients with xanthomatous biliary cirrhosis may also exhibit deep brown pigmentation. Hemochromatosis, however, occurs mainly in males while xanthomatous biliary cirrhosis has so far been reported with one exception only in females.[2] In xanthomatous biliary cirrhosis the extremely high cholesterol and lecithin values are observed at the very beginning of the disease while in these rare cases of hemochromatosis with skin xanthoma, the elevation of the serum lipids and the xanthoma formation occur in the last stages.

The liver and spleen in the generalized form of eosinophilic xanthomatous granuloma (Schüller-Christian's syndrome, normocholesteremic xanthomatosis, lipid granuloma, eosinophilic granuloma) may also be enlarged. In these cases jaundice is never present. The involvement of liver and spleen in this group of "normocholesteremic" xanthomatosis (lipid granulomatosis, eosinophilic xanthomatous granuloma) is part of a systemic granulomatous disorder, which may also comprise skin, lymph glands, lung, bones, dura, and liver. In xanthomatous biliary cirrhosis, however, the liver is the primary seat of the disease resulting in jaundice, hepatosplenomegaly, outstanding accumulation of cholesterol and lecithin in the serum. Xanthoma formation of the skin as well as xanthoma formation of the inner lining of the arteries and in rare cases also of the inner lining of the large bile ducts are secondary to the liver disorder. Neither single foam cells nor nests of foam cells, however, are found in the liver tissue itself in xanthomatous biliary cirrhosis.

Therapy: The patient should become a vegetarian since humans do not usually absorb vegetable sterols. All kinds of vegetables, fruits, nuts, salads, cereals and other carbohydrates are allowed. Animal protein should be given only in the form of skimmed milk, egg white (no yolk), or cottage cheese. All animal fats and meat should be eliminated from the diet. Vegetable fats like olive oil, peanut butter, pure vegetable margarine can be used for cooking. A detailed diet has been outlined by Thannhauser.[45]

In addition intramuscular injections of preparations containing all vitamins in ample amounts should be given twice weekly.

This type of diet treatment excludes only the exogenous quota of animal cholesterol but the endogenous production of cholesterol is not influenced and continues. For this reason the therapeutic value of such a diet is limited. The general nutritional condition during the course of the disease, together with the loss of appetite, may impel the physician to deviate from a strict low cholesterol diet. In such instances small portions of lean meat and lean fish may be added twice weekly.

The administration of choline and methionine and other lipotropic substances is not of great value in this disease since neither increased fat transport (low neutral fat in serum) nor a fatty liver is observed in this disease.

Summary

1. Xanthomatous biliary cirrhosis (pericholangiolitic biliary cirrhosis), with plain and tuberous skin xanthomas, was observed in five cases. The clinical features, the clinical course and the pathology of the disease as visualized in early biopsies and autopsies are described.

2. The clinical syndrome consists of: (*a*) Skin xanthomas of the "plain and tuberous" variety; (*b*) enlarged liver and spleen; (*c*) obstructive type of jaundice of years' duration; (*d*) extremely high values for total cholesterols (four to eight times those of normal) as well as for lecithin (four to

10 times those of normal in the serum; (*c*) low values of neutral fat in the serum. The serum is transparent and not creamy.

3. The anatomical findings in the early biopsies at the time when the extremely high cholesterol and lecithin values are present in the serum are as follows: (*a*) non-specific, chronic inflammatory reaction centered about the smallest bile ducts and junction ducts in the portal areas; (*b*) blocking of the finest bile ducts and subsequent intralobular bile stasis; (*c*) lack of involvement of large bile ducts; (*d*) absence of foam cells in the liver tissue. The anatomical designation "Pericholangiolitic biliary cirrhosis with plain and tuberous skin xanthoma" is proposed for this clinical syndrome under discussion.

4. The etiology of the disease is discussed. Two possibilities for the etiology are debated: (*a*) The excessively high content of the serum cholesterols and lecithins may be caused only by retention resulting from obstruction of the finest bile capillaries and junction ducts; (*b*) increased new formation of cholesterol and lecithin by the liver together with impaired excretion resulting from the obliteration of the finest bile ducts and junction ducts may be responsible for the clinical features of the syndrome. Various laboratory findings and clinical features of the described cases are in favor of the second explanation of the disease.

5. The disease so far is observed mainly in females. There is no familial occurrence of the disease. It should, therefore, not be classified as formerly suggested [14, 15] under the group of essential xanthomatosis of the hypercholesteremic type (hypercholesteremic familial xanthomatosis). Xanthomatous biliary cirrhosis (pericholangiolitic biliary cirrhosis) is a liver disorder and a disease entity by itself.

6. The differential diagnosis of the disease has been discussed.

BIBLIOGRAPHY

1. Addison, T., and Gull, W.: On a certain affection of the skin, vitiligoidea—(*a*) plana; (*b*) tuberosa with remarks, Guy's Hosp. Rep., 1851, vii, 265.
2. Moxon: Jaundice and xanthelasma, Trans. Path. Soc. London, 1873, xxiv, 129.
3. Pye-Smith, P. H.: Xanthelasma of skin, peritoneum and mucous membrane associated with jaundice, Trans. Path. Soc. London, 1873, xxiv, 250.
4. Hutchinson, J., Sangster, A., and Crocker, H. R.: Report on cases of xanthoma multiplex brought before the pathological society by James Startin and S. Mackenzie, Trans. Path. Soc. London, 1881–1882, xxxiii, 376.
5. Balzer, F.: Sur l'etiolige de xanthoma, Arch. de physiol. norm. et path., 1884, iv, 65.
6. Hardaway, W.: Disappearance of extensive eruption of xanthoma, Jr. Cutan. and Genito-Urin. Dis., 1890, viii, 21.
7. Futcher, T. B.: Xanthelasma and chronic jaundice, Am. Jr. Med. Sci., 1905, cxxx, 939.
8. Posner, O.: Beitrag zur Kenntnis der symptomatischen Xanthome bei chronischen Ikterus, Deutsch. med. Wchnschr., 1907, xxxv, 26.
9. Chvostek, F.: Xanthelasma und Icterus, Ztschr. f. klin. Med., 1911, lxxiii, 476.
10. Dyke, S. C.: Hypercholesterolaemic splenomegaly, Jr. Path. and Bact., 1928, xxi, 173.
11. Weidman, F. D., and Freeman, W.: Xanthoma tuberosum; two necropsies disclosing lesions of central nervous system and other tissues, Arch. Dermat. and Syph., 1924, ix, 49.

12. Buerger, M.: Klinik der Lipoidosen, Neue deutsche Klinik, xii, 528 Urban u. Schwarzenberg, Berlin, 1934.
13. Weidman, F. D., and Boston, L. N.: Generalized xanthoma tuberosum with xanthomatous changes in fresh scars of intercurrent zoster; adenocarcinoma of ampulla of Vater at necropsy, Arch. Int. Med., 1937, lix, 793.
14. Thannhauser, S. J., and Magendantz, H.: The different clinical groups of xanthomatous diseases: a clinical, physiological study of 22 cases, Ann. Int. Med., 1938, xi, 1662.
15. Thannhauser, S. J.: Lipidoses, 1940, Oxford University Press, p. 107.
16. Comfort, M. W., Shepard, V. H., and Snell, A. M.: Xanthomatous biliary cirrhosis, Proc. Staff Meet. Mayo Clin., 1941, xvi, 374.
17. Herbert, F. K.: Case of juvenile xanthomatosis, Arch. Dis. Child., 1943, xviii, 41.
18. Eusterman, G. B., and Montgomery, H.: Disorders of the liver and the extrahepatic biliary ducts associated with cutaneous xanthoma and hyperlipemia, Gastroenterology, 1944, iii, 275.
19. Layani, F., Laudat, M., and Astruc, P.: Sur un cas de maladie xanthomateuse, Bull. et mém. Soc. méd. d. hôp. de Paris, 1939, lv, 355.
20. Hoffbauer, F. W., Evans, G. T., and Watson, C. J.: Cirrhosis of the liver presenting the clinical features of xanthomatous biliary cirrhosis but with confirmation at autopsy, Med. Clin. N. Am., 1945, 1054.
21. Hoffbauer, F. W., Evans, G. T., and Watson, C. J.: Cirrhosis of the liver with particular reference to correlation of composite liver function studies with liver biopsies, Med. Clin. N. Am., 1945, 363.
22. Gebhardt, M. C.: Xanthomatous biliary cirrhosis. Lipid levels while receiving inositol, Arch. Int. Med., 1947, xxvi, 1947.
23. Fagge, C. H.: General xanthelasma or vilitigoidea, Trans. Path. Soc. London, 1872–1873, xxiv, 242.
24. Thannhauser, S. J., and Schmidt, G.: Lipins and lipidoses, Physiol. Rev., 1946, xxvi, 275.
25. Epstein, E. Z., and Greenspan, E. B.: Clinical significance of cholesterol partition in hepatic and biliary diseases, Arch. Int. Med., 1936, lviii, 860.
26. Gibson, W. R., and Robertson, H. E.: So-called biliary cirrhosis, Arch. Path., 1939, xxviii, 37.
27. Thannhauser, S. J.: Serum lipids and their value for diagnosis, New Eng. Jr. Med., 1947, ccxxxvii, 515.
28. Thannhauser, S. J., and Schaber, H.: Kann der tierische organismus cholesterin synthetisieren? Ztschr. f. physiol. Chem., 1923, cxxvii, 278.
29. Cantarow, A., and Bucher, C. J.: Biliary stasis and decompression; review of recent contributions, Internat. Clin., 1938, I, 272.
30. Müller, C.: Angina pectoris in hereditary xanthomatosis, Arch. Int. Med., 1939, lxiv, 675.
31. Duchosal, P. W., and Rutishauer, A.: Demonstration de cas et familaux de gautte lipidque, sporadique, Helvet. med. acta, 1943, x, 223.
32. Engelberg, H., and Newman, B. A.: Xanthomatosis. A cause of coronary artery disease in young adults, Jr. Am. Med. Assoc., 1943, cxxii, 1167.
33. Watson, C. J., and Hoffbauer, F. W.: The problem of prolonged hepatitis with particular reference to the cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver, Ann. Int. Med., 1946, xxv, 195.
34. Holt, L. E., Aylward, F. X., and Timbres, H. G.: Idiopathic familial hyperlipemia, Bull. Johns Hopkins Hosp., 1939, lxiv, 279.
35. Holt, L. E., Aylward, F. X., and Timbres, H. G.: Familial lipemia of undetermined origin, Jr. Clin. Invest., 1936, xv, 451.
36. Goodman, M., Shuman, H., and Goodman, S.: Idiopathic lipemia with secondary xanthomatosis, hepatosplenomegaly and lipemic retinalis, Jr. Pediat., 1940, xvi, 596.

37. THANNHAUSER, S. J.: Lipidoses, 1940, Oxford University Press, p. 179.
38. BUERGER, M., and GRÜTZ, O.: Über hepatosplenomegale Lipoidose mit xanthomatosen Veranderungen in Haut und Schleimhaut, Arch. f. Dermat. u. Syph., 1932, clxvi, 542.
39. BERNHARD, E.: Ueber einen Fall von Lipämie, Schweiz. med. Wchnschr., 1936, lxvi, 261.
40. JOEL, E.: Pancreatic lipemia, Ztschr. f. klin. Med., 1924, c, 46.
41. MARCUS, M.: The pancreas and the intermediate metabolism, Folia. clin. orient., 1937, I, 127.
42. BEUMER, H., and LOSCHKE, H.: Zum Stoffwechsel und zur differential Diagnose der Glykogenspeichenkrankheit, Munchen. med. Wchnschr., 1933, lxxx, 377.
43. BEUMER, H.: Ueber der Cholesterinstoffwechsel bei der Glykogenspeicherkrankheit, Munchen. med. Wchnschr., 1937, lxxxiv, 1007.
44. THANNHAUSER, S. J.: Lipidoses, 1940, Oxford University Press, p. 223.
45. THANNHAUSER, S. J.: Lipidoses, 1940, Oxford University Press, p. 110.
46. HOLDEN, R., and THANNHAUSER, S. J.: Idiopathic hyperlipemia with and without slight glycosuria and eruptive xanthoma. To be published.
47. THANNHAUSER, S. J., and REINSTEIN, H.: Fatty changes in the liver from different causes, Arch. Path., xxxiii, 646.
48. MACMAHON, H. E., and MALLORY, F. B.: Obstructive cirrhosis, Am. Jr. Path., 1929, v, 645.
49. MACMAHON, H. E.: Infectious cirrhosis, Am. Jr. Path., 1931, vii, 77.
50. DEUTSCH, E., and MACMAHON, H. E.: Epidemic hepatitis, Gastroenterology, 1947, viii, 311.
51. MACMAHON, H. E.: Biliary xanthomatosis (xanthomatous biliary cirrhosis), Am. Jr. Path., 1948, xxiv, 527.

CASE REPORTS

Q FEVER: REPORT OF A CASE IN PENNSYLVANIA*

By O. Henry Janton, M.D., Amedeo Bondi, Jr., Ph.D., and M. Michael Sigel, Ph.D., *Philadelphia, Pennsylvania*

The purpose of this paper is to present a serologically proved case of Q fever and reëmphasize the importance of considering this disease in the diagnosis of non-bacterial pneumonias. This case is of further interest because we feel that it is the first report of Q fever naturally acquired in Pennsylvania, as well as in eastern United States.

Case Report

W. W., a white male, age 36, was admitted to the Hahnemann Hospital February 9, 1948, complaining of chills and fever of one day's duration. The patient stated that he had felt well until 7:00 p.m., February 8, 1948 when he experienced a sudden chill which lasted the entire evening. He was awakened at midnight with chills and tried to keep warm by covering himself with additional blankets but to no avail. On arising at 6:00 a.m. on the ninth, he ached all over but decided to go to work. The patient worked at his job in a wool-processing factory until 3:00 p.m. when he was forced to leave because of generalized weakness and aching. Towards evening he became chilly again and feverish. A slight productive cough was present consisting of white phlegm. At no time was the sputum blood tinged. At the time of admission the same evening he complained of a headache and pain in the back and left chest, this latter pain having no relation to respiration. The history was negative for hemoptysis, chronic cough, dyspnea, night sweats and weight loss.

The past history was essentially negative except for an attack of "flu" in 1918; appendectomy, 1936; and a nasal operation, 1938.

Physical examination revealed a well developed young adult male. He was well oriented but appeared acutely ill with a red flushed face and hot dry skin. There was no evidence of dyspnea, cyanosis, edema, pallor, jaundice or glandular enlargement. The temperature was 103.2° F., the pulse 100, the respirations 20 and the blood pressure 140 mm. Hg systolic and 84 mm. diastolic. The nasal mucosa was injected and a mucopurulent discharge was present. Marked injection of the throat, and a postnasal discharge were observed. Examination of the lungs failed to demonstrate any consolidation, râles or other abnormalities. The remainder of the examination was essentially negative. A persistent headache prevented him from sleeping. The patient was given 30,000 units of crystalline penicillin G in aqueous solution intramuscularly every three hours; 0.6 gm. of aspirin was also given.

On awakening February 10, 1948, he again complained of a headache and sore throat accompanied by a chilly feeling and general aching. Saline throat irrigations and neosynephrine 0.25 per cent three drops in each nostril every four hours were ordered. That afternoon the patient had a chill and became very toxic with increase

* Received for publication September 11, 1948.

From the Departments of Medicine and Bacteriology, Hahnemann Medical College and Hospital and the Children's Hospital of Philadelphia (Department of Pediatrics, School of Medicine, University of Pennsylvania), Philadelphia, Pennsylvania.

The experimental work described in this paper was aided by the office of Naval Research.

in the severity of the headache. Examination revealed a markedly reddened pharynx. There were increased breath sounds at the left lung base and questionable tubular-like breath sounds at the right base. The roentgenogram of the chest was reported as "some accentuation of the bronchovascular shadows throughout the mesial aspect of both lung fields." Codeine sulfate, 0.3 gm., was given to control the headache. Profuse sweating developed and coughing increased. The dosage of penicillin was raised to 50,000 units every three hours.

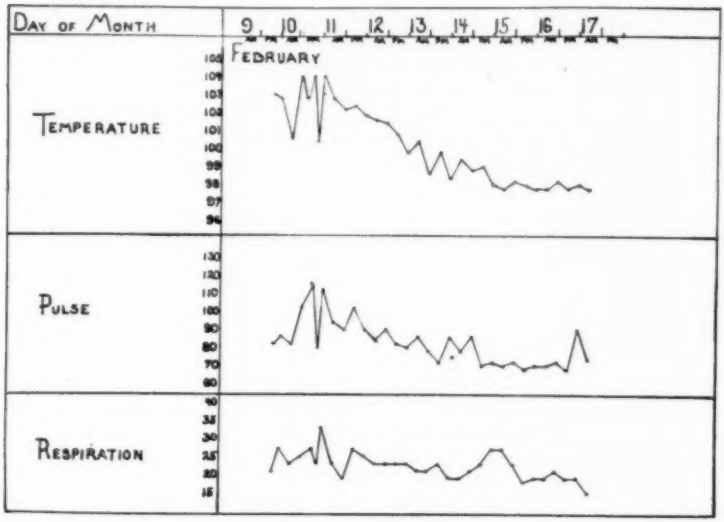


Fig. 1. Clinical chart.

The patient remained acutely ill for the next two days; physical findings remained essentially unchanged except for the presence of a few coarse râles throughout both the lung fields which cleared for the most part after coughing.

On February 13, a considerable improvement in the patient's condition was observed. His headache diminished in severity and finally disappeared. The inflammation of the pharynx began to subside; all lung fields were clear to auscultation and the temperature had begun to fall. From this day until his discharge on February 17, 1948, clinical improvement both objectively and subjectively proceeded rapidly, the temperature falling by lysis and reaching normal by the fifteenth. At the time of discharge, the patient ate well, had no headache, pains or cough.

The total dosage of penicillin administered from February 9 to February 16 was 2,580,000 units without apparent benefit to the patient.

Laboratory Findings

Urinalysis on admission was negative. Blood studies revealed a red cell count of 4,280,000, hemoglobin 13.7 gm., white cells 5,000 with 80 per cent polymorphonuclear cells and 20 per cent lymphocytes. Throughout the illness the

blood picture remained more or less constant. The electrocardiogram was normal. Bacteriological studies of the throat failed to demonstrate a pathogenic organism at any time. The spinal fluid study was normal. Stool examination was negative for occult blood, ova and parasites. The blood urea nitrogen and blood sugar were normal. Wassermann and Kahn tests of blood and spinal fluid were negative. Agglutination tests with the typhoid O and H, paratyphoid A and B, Proteus OX 19 and *Br. abortus* were negative.

Tests on the patient's sera taken shortly after onset and at several intervals during the course of the disease as well as following recovery were carried out at the Virus Diagnostic Research Laboratory at the Children's Hospital of Philadelphia. These consisted of: Complement fixation tests with the antigens of influenza virus types A and B, as well as the tests used routinely by this laboratory for the diagnosis of atypical pneumonia, i.e., complement fixation with an antigen of the psittacosis-lymphogranuloma group of agents and the antigen of Q fever rickettsia (American strain) and the cold agglutination test. The results are tabulated below.

Date	Influenza A	Influenza B	Psittacosis-L.G.V.	Cold Agglutinins	Q Fever
Feb. 11	<1:4	<1:4	<1:10	1:80	<1:2
Feb. 17			<1:10	1:80	1:16
Feb. 18	<1:4	<1:4		1:80	1:16
May 13					1:256
June 8					1:256*

* This result obtained with the American strain of Q fever rickettsia was confirmed by Dr. H. Koprowski of the Lederle Laboratories using the Italian strain.

The results above reveal that the patient developed antibodies against the rickettsia of Q fever and not against the pneumotropic viruses. The presence of cold agglutinins is not considered significant since they were present in the serum taken three days after onset and since they failed to rise in titer. The finding of an increasing titer of antibodies to the Q fever rickettsia established a definite diagnosis of Q fever.

Comment

The significant clinical features of this case were: The explosive onset with chills, headache of such severe and persistent character that the diagnosis of meningitis was entertained, marked upper respiratory manifestations with minimal clinical and no roentgenological evidence of lung involvement. The course was a febrile one with a fastigium of temperature between 101° and 104° F., which fell spontaneously by lysis and was unaffected by penicillin. The white cell count remained normal throughout.

The above clinical findings initially suggested the diagnosis of an atypical pneumonia or influenza, but the course and subsequent clinical findings failed to support a diagnosis of the former; although in retrospect they were compatible with what other authors have described in proved cases of Q fever. This illustrates the need for laboratory aid in differentiating the etiological entities grouped clinically under the heading influenza, grippe or atypical pneumonia.

The signs, symptoms and roentgen-ray findings of Q fever described in the outbreak at the National Institute of Health [1] were those of atypical pneumonia.* Atypical pneumonia also constituted an important feature of the first proved infection that was acquired naturally in the United States,[2] and in the various groups of cases studied by the Army [3] as well as the Amarillo epidemic.[4, 5, 6] Pulmonary lesions, however, have not been observed as a prominent feature of Australian Q fever.[7] Recent literature [4, 8, 9, 10, 11] has revealed the increasing incidence of Q fever in circumscribed areas of western, midwestern and southwestern United States. So far this infection has seemingly been found chiefly in packing house and slaughterhouse workers, dairy farmers and laboratory personnel. Isolated cases in all instances could be traced to exposure in a known endemic area.[12] Although it is an accepted fact that the organism, *Rickettsia burneti,* is present in the feces of certain arthropod vectors,[13, 14, 15] the actual method of transmission of the disease to man is uncertain.[16] There was a history of tick bite in some American cases that developed in areas where the rickettsia of Q fever has been found.[17] Careful epidemiologic studies carried out during the Amarillo, Texas epidemic [4, 5, 6] and elsewhere,[12] inconclusively attribute the acquisition of the infection to inhalation of contaminated dust. Of considerable interest is the occurrence of a number of proved cases of Q fever in the vicinity of Los Angeles, California and the isolation of the etiological agent from raw milk.[8] Although the rickettsia were recovered from raw milk, the available evidence failed to implicate the drinking of the milk as the cause of the infection. Huebner and his associates, however, believe that infected milk may serve as a source of infection by some mechanism not yet known.

The mode of infection in our patient is not certain. However, it is known that he handled wool and animal hair in a dusty atmosphere, and that subsequently other cases of Q fever were found in the same factory.[18] Thus it seems probable that the infecting agent was carried by these materials and entered through the respiratory tract.

The case is of importance in emphasizing the need for an accurate diagnosis of the etiology of influenza-like illnesses, or atypical pneumonia, particularly in view of the recent advent of antibiotics effective against rickettsia.[19, 20]

Summary

The first report of a serologically authenticated case of naturally acquired Q fever in eastern United States is presented. The clinical features are discussed in detail with emphasis placed on the consideration of this disease in the differential diagnosis of respiratory disorders. The possible mode of transmission is discussed.

BIBLIOGRAPHY

1. Hornibrook, J. W., and Nelson, K. R.: An institutional outbreak of pneumonitis. I. Epidemiological and clinical studies, Pub. Health Rep., 1940, lv, 1936–1944.
2. Hesdorffer, M. B., and Duffalo, J. A.: American Q fever: report of a probable case, Jr. Am. Med. Assoc., 1941, cxvi, 1901–1902.

* Aware of the fact that pulmonary infiltration occasionally occurs late in this infection, subsequent roentgen-rays were done on this patient and were found to be normal.

3. Robbins, F. C., and Ragan, C. A.: Q fever in the Mediterranean area: reports of its occurrence in allied troops. I. Clinical features of the disease, Am. Jr. Hyg., 1946, xliv, 6–22.
4. Topping, N. H., Shepard, C. C., and Irons, J. V.: Q fever in the United States. I. Epidemiological studies of an outbreak among stock handlers and slaughterhouse workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 813–815.
5. Irons, J. V., and Hooper, J. M.: Q fever in the United States. II. Clinical data on an outbreak among stock handlers and slaughter-house workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 815–818.
6. Irons, J. V., Murphy, J. N., and Wolfe, D. M.: Q fever in the United States. III. Serologic observations in an outbreak among stock handlers and slaughterhouse workers, Jr. Am. Med. Assoc., 1947, cxxxiii, 818–820.
7. Derrick, E. H.: "Q" fever, a new fever entity: clinical features, diagnosis, and laboratory investigation, Med. Jr. Australia, 1937, ii, 281–289.
8. Heubner, R. J., Jellison, W. L., Beck, M. D., Parker, R. R., and Shepard, C. C.: Q fever studies in Southern California, Pub. Health Rep., 1948, lxiii, 214.
9. Shepard, C. C., and Huebner, R. J.: Q fever in Los Angeles County, Am. Jr. Pub. Health, 1948, xxxviii, 781–788.
10. Strauss, E., and Sulkin, S. E.: Studies on Q fever: Complement-fixing antibodies in meat packers at Fort Worth, Texas, Proc. Soc. Exper. Biol. and Med., 1948, lxvii, 139–141.
11. Shepard, C. C.: An outbreak of Q fever in a Chicago packing house, Am. Jr. Hyg., 1947, xlvi, 185–192.
12. Editorial: Q fever, Ann. Int. Med., 1948, xxxiii, 154–162.
13. Davis, G. E., and Cox, H. R.: A filter-passing infectious agent isolated from ticks. I. Isolation from *Dermacentor andersoni*, reactions in animals and filtration experiments, Pub. Health Rep., 1938, liii, 2259–2267.
14. Parker, R. R., and Davis, G. E.: A filter-passing infectious agent isolated from ticks. II. Transmission by *Dermacentor andersoni*, Pub. Health Rep., 1938, liii, 2267–2270.
15. Cox, H. R.: A filter-passing infectious agent isolated from ticks. III. Description of organism and cultivation experiments, Pub. Health Rep., 1938, liii, 2270–2276.
16. Finland, M., and Lesses, M. F.: Q fever, N. Eng. Jr. Med., 1947, ccxxxvii, 255–258.
17. Cox, H. R.: *Rickettsia diaporica* and American Q fever, Am. Jr. Trop. Med., 1940, xx, 463–469.
18. Sigel, M. M., McNair-Scott, T. F., Janton, O. H., and Henle, W.: In preparation.
19. Smadel, J. E., Woodward, T. E., Ley, H. L., Jr., Philip, C. B., and Traub, R.: Chloromycetin in the treatment of scrub typhus, Science, 1948, cviii, 160–161.
20. Smadel, J. E., Leon, A. P., Ley, H .L., Jr., and Varela, G.: Chloromycetin in the treatment of patients with typhus fever, Proc. Soc. Exper. Biol. and Med., 1948, lxviii, 12–19.

DIFFUSE MELANOSIS, PERICARDIAL EFFUSION, AND MELANURIA ASSOCIATED WITH MALIGNANT MELANOMA: CASE REPORT WITH AUTOPSY FINDINGS*

By Norton D. Ritz, M.A., M.D., *Brooklyn, New York*

The literature pertaining to malignant melanoma is voluminous. The following case is reported because of its unusual association of diffuse melanosis

* Received for publication March 31, 1947.
From the service of Dr. Henry M. Feinblatt, Director of Medicine, Kings County Hospital, New York, N. Y.

of the skin, cardiac metastases, massive pericardial effusion, and melanuria in the same patient, all secondary to a melanoma on the forearm.

Case Report

F. R., a 47 year old American-born laborer and hide-sorter, entered the hospital on June 30, 1946, because his face "was turning all kinds of colors." Eight months prior to admission a flat mole the size of a dime on his right forearm had begun to enlarge and become blacker. In March, 1946, he had noted a lump in his right axilla. Hospitalization was advised by his doctor at that time but refused by the patient. Meanwhile, the mole on his arm continued to enlarge. Three or four weeks before entering the hospital he had noticed multiple subcutaneous nodules and increasing pigmentation of the face, neck, and hands. Dyspnea on exertion, hemoptysis, anorexia, and a weight loss of 10 pounds had also occurred during this time. His urine had become dark brown in color.

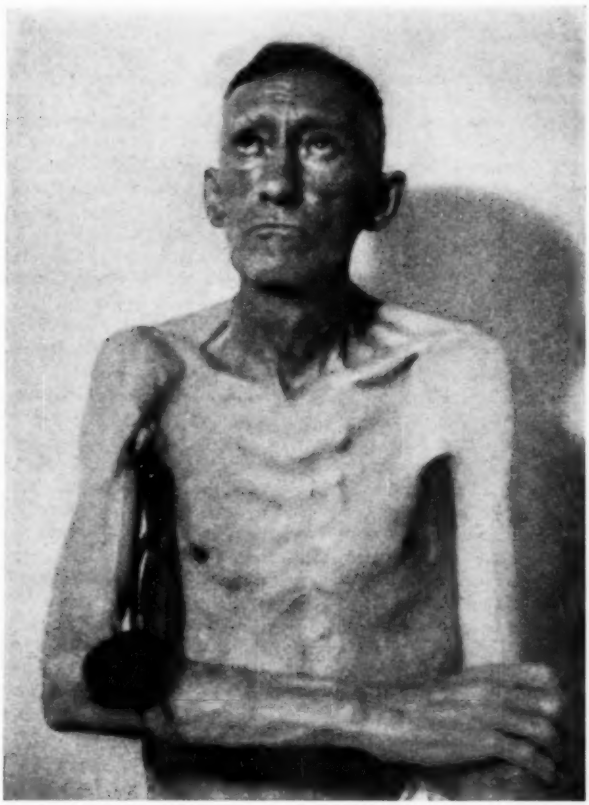


Fig. 1. Primary lesion on forearm, subcutaneous metastases, and melanosis of face and neck.

Prior to the present illness he had always been in good health. He had consumed about one quart of beer daily during the past few years. There was no history of his using any silver preparations or of any recent exposure to the sun.

Physical examination revealed an emaciated, poorly-developed white man, temperature 100° F., pulse 100, respirations 20. His face and neck were a bluish-black gun-metal color, fading to a light brown over the upper extremities and trunk, then to a normal color over the lower trunk and lower extremities. There were multiple hard subcutaneous nodules scattered over the entire trunk and both arms; these appeared to have a black color where near the surface. One nodule had broken through the skin on the anterior left thigh just below the inguinal ligament to form an oval, flat, black papule, 1 cm. in diameter. On the right forearm there was a large fungating black mass about 5 cm. in diameter and 3 cm. above the surface of the skin. The surrounding area was brownish-black in color for one-quarter to one-half inch about the base of the lesion. The mass was friable, grossly infected, and bled easily, although not appearing painful (figure 1).

The sclerae had a brownish tinge. Funduscopic examination revealed no abnormalities. The mucous membranes of the mouth and nose had a bluish-brown color. The teeth were carious, with somewhat hypertrophied gums, also bluish in color. The drumheads appeared normal. The neck veins were distended; there were stony hard nodes in the cervical and both supraclavicular regions. Similar nodes were evident in both axillary and inguinal regions. The chest was clear except for a few moist râles audible over the right middle lobe. The heart did not appear enlarged at this time. The rhythm was regular, the tones were of good quality, and no murmurs were audible. Blood pressure was 126 mm. Hg systolic and 90 mm. diastolic. A hard tender liver edge was palpated three fingers'-breadth below the right costal margin. The spleen was not palpable. A diagnosis of melanoma with generalized metastases was made.

Laboratory Data. The urine was dark brown, specific gravity 1.018, acid reaction, negative for albumin and sugar. There was a 4 plus positive test for melanin using ferric chloride. Microscopic examination revealed 2 to 3 leukocytes per high power field, a rare red blood cell and no casts. There were 8150 white blood cells per cu. mm. with a differential of 54 polymorphonuclears, four band forms, two eosinophiles, one monocyte, three basophiles, and 36 lymphocytes. Red blood cells numbered 4.0 million; the hemoglobin (Sahli) was 12.4 gm. The Wassermann test was negative. Blood urea was 30 mg. per cent, sugar 88 mg. per cent, icteric index 10. Total cholesterol was 138 mg. per 100 c.c. of serum, free cholesterol 78 mg., esters 60 mg. per cent. On July 19, blood sugar was 76 mg. per cent, plasma sodium 322 mg. per cent, and potassium 25 mg. per cent. On July 22, the thymol turbidity test was negative, total protein 4.4 gm. per 100 c.c. plasma, and alkaline phosphatase blood level 5.8 units.[1] Calcium and phosphorus levels were 11.6 mg. and 3.9 mg., respectively. A bromsulfalein test on July 23 was lost because of hemolysis.

Course. Proctoscopy on July 3 revealed no lesions or evidence of pigment deposition in the rectosigmoid.

Biopsy of the lesion on the right forearm was reported as follows: "Section of skin biopsy shows a malignant invading neoplasm made up of heavily pigmented, polyhedral, spindle cells invading the connective tissue. The nuclei vary markedly in morphology and staining, and in some instances the cells are so heavily occupied by melanin that the morphology cannot be distinguished." The histologic diagnosis was malignant melanoma.

Liver punch biopsy on July 8 showed swelling and vacuolization of the cytoplasm of the liver cells. In the pericentral zone area and in some of the Kupffer cells there was a light-brown pigment interpreted as melanin deposition in the liver.

Roentgen-rays taken on July 11 revealed enlargement of the cardiac shadow in all its diameters, with a configuration suggestive of pericardial effusion and evidence of metastatic lesions in both basilar lung fields (figure 2). There were no metastases to the long bones, but one suspicious area of decreased density was present in the skull.

It was observed that the cardiac dullness had increased to the left mid-axillary line, whereas the point of maximal impulse remained in the mid-clavicular line. The tones were of fair quality. Rotch's and Ewart's signs were negative; the pulse was not paradoxical. However, the neck veins remained distended and the liver was palpable three fingers'-breadth below the right costal margin. One plus edema of the ankles was noted for the first time. Fluoroscopy and roentgenkymograms confirmed the impression of pericardial effusion. An electrocardiogram on July 12 showed a sinus tachycardia, rate 106, low voltage of ventricular complexes, low R_4, with

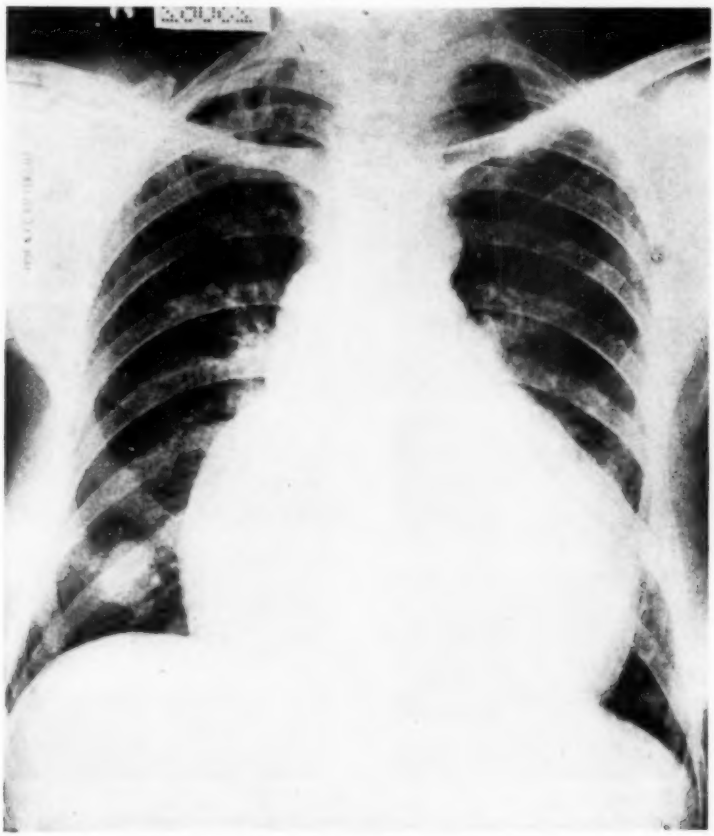
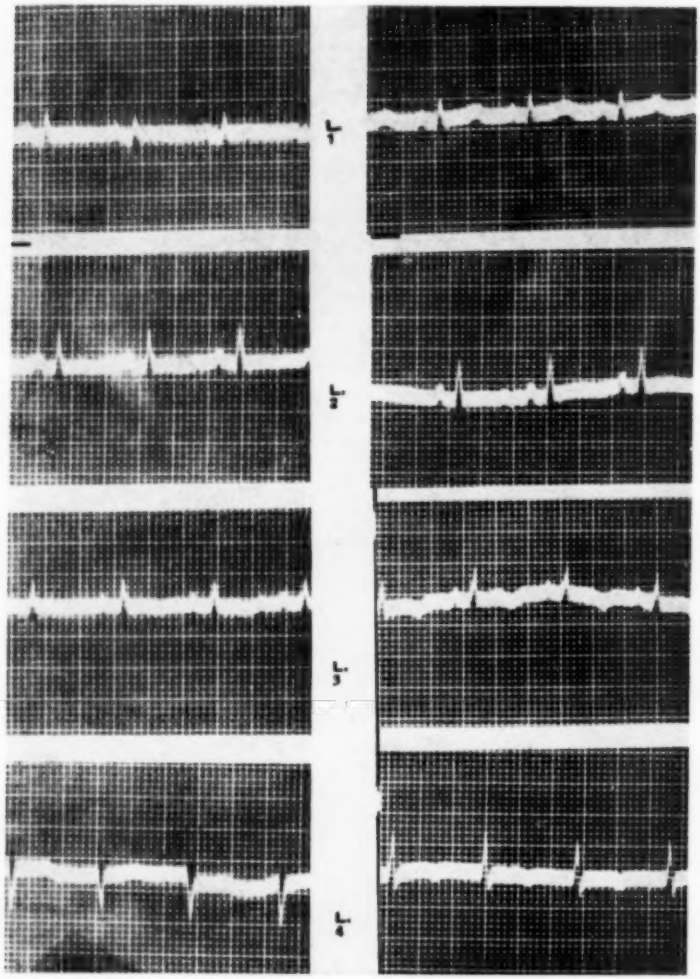


FIG. 2. Flask-shaped configuration of cardiac silhouette; metastases to lungs.

T-waves isoelectric in Leads I and IV (CF_4) and semi-inverted in Leads II and III (figure 3*a*).

The patient began to complain of marked anorexia and substernal discomfort Characteristically, he obtained some relief by leaning forward in bed.



(*a*) (*b*)

FIG. 3. Electrocardiograms (*a*) July 12, 1946. Low voltage of QRS complexes, low R_4; isoelectric T_1 and T_4; semi-inversion of T_2 and T_3. (*b*) July 27, 1946. Low voltage of QRS complexes; isoelectric T_3; inverted T_2 and T_4.

At this time the decholin circulation time was 23 seconds. The venous pressure was 21 cm. of water, rising to 24 cm. on liver pressure, and returning to 22 cm.

Pericardial tap was performed on July 19, by the left paraxiphoid approach, with the removal of 600 c.c. of a brownish-tinged, clear fluid. Blood pressure before the paracentesis was 111/98; immediately thereafter, it was 108/88. The patient experienced considerable relief. Dyspnea and edema decreased, and his neck veins became flat for the first time since admission. The fluid had a specific gravity of 1.009; there were 1800 cells per cu. mm., predominantly crenated red blood cells. A few polymorphonuclears and large macrophages containing brownish pigment were also present. The protein content was 980 mg. per 100 c.c. No malignant cells were noted in the cell block. The following day the patient appeared much improved. However, the liver did not recede; the spleen was palpated two fingers below the left costal margin for the first time.

On July 26, because of signs of increasing tamponade, pericardial tap was again performed. The blood pressure was now 94/80. Only 75 c.c. of slightly sanguinous fluid were withdrawn. A cell block of this fluid showed numerous polymorphonuclears, red blood cells, occasional lymphocytes and macrophages, and polyhedral cells containing dark brown pigment in the cytoplasm. The block was interpreted as positive for malignant cells.

A repeat electrocardiogram on July 27 again demonstrated low voltage of QRS complexes with isoelectric T_2 and inverted T_3 and T_4. The findings were compatible with pericardial involvement (figure 3*b*).

A third pericardial tap was carried out on July 29, when 750 c.c. of sanguinous fluid were removed through a needle inserted in the fifth interspace at the anterior axillary line and 300 c.c. of filtered air were injected. Blood pressure before the procedure was 92/84; immediately thereafter, it was 100/92. On the same day, because of signs of fluid in the chest, thoracentesis was performed in the ninth interspace in the midscapular line, and 650 c.c. of a sanguinous fluid similar in appearance to the pericardial fluid were obtained. Cell blocks of both fluids revealed no malignant cells; pigment laden macrophages were again seen. The patient obtained temporary symptomatic relief from these procedures but continued to go downward. Roentgen-rays of the chest on July 30 demonstrated a hydropneumopericardium and a left hydropneumothorax with well-visualized fluid levels.

The pericardial and pleural fluid rapidly reaccumulated. On August 1 the patient died.

Urinary Studies. A heavy black precipitate formed on the addition of ferric chloride or bromine water which could be dissolved by sodium carbonate solution and reprecipitated by the addition of acid, thus satisfying the criteria [2] for melanin.

The urine did not become dark on the addition of alkali, nor did it reduce Benedict's solution, ruling out alkaptonuria.

Thormählen's [3, 4] test for melanin was strongly positive. This is performed similarly to the Legal test for acetone. A few drops of 5 per cent sodium nitroprusside are added to 3 to 5 c.c. of urine, and then a few drops of 10 per cent sodium hydroxide. At this point a deep ruby color results, which may also be given by acetone and creatinine. However, acidification with glacial acetic acid causes an immediate azure-blue color. Acetone, on the other hand, turns deeper red; creatinine turns yellow, then slowly green, and finally blue.

Estimation of the 24-hour output of melanin in the urine by the method of Blackberg and Wanger [5] on two successive days yielded 0.43 gm. and 0.47 gm. of melanin. This method is based on the precipitation of melanin from the urine, solution in 5 per cent sodium hydroxide, then reprecipitation with 0.1N HCl, filtering and weighing.

Abstract of Autopsy Protocol. The body is that of a white male measuring 67 inches and weighing approximately 115 lbs. The skin is dry and markedly pig-

mented, especially the facial and neck areas. Numerous small, firm, subcutaneous nodules are present, measuring 2 to 10 mm., many of which are fixed and attached to the underlying tissue. A large black fungating tumor mass is present on the anterior aspect of the mid-right forearm measuring 6 by 5 by 3 cm. The right sclera is mildly pigmented a light-brown color, but there is no evidence of jaundice or petechiae. The liver and spleen are palpable three fingers below the costal margins.

FIG. 4. Melanotic metastases to epicardium and myocardium.

On making the incision, there are numerous black, firm, discrete nodules seen throughout the subcutaneous tissue. The peritoneal serosal surfaces are smooth and glistening; there are tumor nodules throughout the abdomen, especially involving the peri-aortic lymph nodes. Numerous small, black, discrete nodules are present on both

pleural surfaces. About 500 c.c. of dark brown fluid are present in the left pleural cavity. Fibrous adhesions are noted at both apices. About 1000 c.c. of dark brown clear fluid are present in the pericardial sac. The pulmonary artery is opened in situ and no evidence of embolus is found.

The heart weighs 380 gm. The epicardium is studded with numerous black nodules varying up to 1 cm. in diameter (figure 4). Lying within the right atrium and its appendage is a large black friable tumor thrombus which is firmly adherent to the endocardial surface. The tricuspid orifice is almost occluded. At the apex of the left ventricle, a small firm adherent mural antemortem blood thrombus is present. The myocardium on cut section is pale red with diffuse brown speckling. Several small tumor nodules are noted scattered throughout the myocardium. The coronary arteries are patent (figure 5).

The lungs reveal dense fibrous adhesions at both apices. The left lower lobe is atelectatic as a result of fluid compression of the left pleural cavity. Scattered

FIG. 5. Melanotic tumor thrombus in right atrium and appendage; metastases in myocardium.

throughout the lung parenchyma are numerous black, firm, discrete tumor nodules. The hilar, tracheobronchial, and para-esophageal lymph nodes are markedly involved by melanotic tumor.

The spleen weighs 1200 gm. It is black, firm, and almost entirely replaced by tumor.

The liver weighs 1800 gm. The edges are sharp and the organ is diffusely pigmented brown-black. On cut section, several tumor nodules are seen measuring from 8 to 13 mm. The liver is nutmeg in appearance and shows moderate edema of the parenchyma.

In place of the adrenals are two huge, friable, triangular black tumor masses measuring about 5 cm. by 5 cm. by 3 cm. On section of these masses, no gross evidence of adrenal tissue is seen.

The right kidney weighs 180 gm. and the left kidney 200 gm. Numerous tumor nodules are present in the capsule, which strips with ease. The kidney is diffusely pigmented. Tumor has invaded both renal veins.

The submucosa of the duodenum and entire small intestine is studded with small, black, discrete tumor nodules, 2 to 5 mm. in diameter.

The right sternal-clavicular joint on cut section is diffusely infiltrated with black melanotic pigment, but the ribs and vertebrae are grossly free. The remaining organs are not remarkable.

Permission for examination of the brain and spinal cord could not be obtained.

Microscopic examination confirmed the presence of metastases in the sites mentioned. There was diffuse infiltration of the liver and spleen by pigmented tumor cells; there was also considerable pigment in the reticulo-endothelial cells. In the kidney, pigment was laid down in a haphazard fashion, but mostly in the epithelium of the collecting and convoluted tubules, which showed cloudy swelling. Pigment-bearing cells were also noted in the diaphragm, prostate, and bone-marrow. There was no recognizable adrenal tissue in histological sections of the tumor masses replacing these glands. The skin of the abdomen showed no increase in melanin pigment; permission to study the skin of the face or neck was not granted.

Anatomical Diagnosis. Melanocarcinoma right forearm, with metastases to lungs, pleura, liver, heart, spleen, adrenals, small intestine, skin, subcutaneous tissue, muscles, bone marrow and paratracheal, hilar, parabronchial, axillary, cervical and inguinal lymph nodes; mural tumor thrombus right auricle.

Melanosis of skin, liver, lungs, heart, kidneys, spleen, adrenals, and intestine. Antemortem blood thrombus left ventricle (apex); left pleural effusion; pericardial effusion; chronic passive congestion of liver.

Melanosis

Although melanoma is a fairly common clinical entity, diffuse melanosis of the skin is of infrequent occurrence. Diffuse melanosis, manifested by diffuse pigmentation, should be distinguished from massive discrete metastases to the skin. The cause of diffuse melanosis is not entirely clear, since there are cases of widespread metastatic involvement frequently seen which do not show melanosis. A patient described by Way and Light[6] manifested thousands of metastatic macules and papules, so numerous as to resemble a purpura hemorrhagica, with secondary skin pigmentation. There were a few small metastatic nodules in the left adrenal gland; the right was not involved. Odel, Montgomery and Horton[7] described a case of melanosis associated with melanuria secondary to a malignant mole over the left scapular region. Their patient had a diffuse blue-gray pigmentation of the skin and mucous membranes; the face was

a deep blue-black color. Dixon [8] also emphasized the "gun-metal or argyria-like color" of his patient. Odel et al. postulated a toxic or metastatic involvement of the suprarenal glands and adjacent chromaffin tissues; this was not proved, since no autopsy was obtained. In Dixon's case, there were minute islands of metastases in both adrenals. In a case of primary melanoma of the left adrenal recently described, there was no melanosis; however, the right adrenal contained only a small tumor nodule.[9] In the author's case, both adrenals were massively involved and almost completely replaced by tumor. No adrenal tissue could be identified microscopically. Nevertheless, as far as could be determined, there was no gross adrenal insufficiency. The blood sugar and plasma sodium were within normal limits; the plasma potassium was slightly elevated. However, even in Addison's disease, there is no constant correlation between degree of pigmentation and severity of systemic manifestations.[10] It is possible that the coexistence of severely damaged adrenals with excessive amounts of melanin in the body facilitates the deposition of pigment in the skin. The low blood pressure can be explained by the massive pericardial effusion. Further studies of adrenal function were unfortunately not undertaken.

The bluish color seen clinically in diffuse melanosis is thought to be due to the deposition of melanin in chromatophores in the corium with a relative absence of melanoblasts in the epidermis. The mechanism is comparable to that in *nevus blau* (blue nevus of Jadassohn), in which the pigment is mostly in melanoblasts in the cutis rather than in the epidermis. As noted by Odel et al.,[7] there may be accentuation of the pigmentation in exposed regions of the skin, particularly the face and neck. This was true in the case described here. Edwards and Duntley [11] have called attention to the rôle of light scattering in the production of skin coloration. The shorter wave-lengths towards the blue end of the spectrum are scattered laterally in the stratum mucosum and then partially reflected, whereas the longer red-wave lengths penetrate to the deeper skin layers, where they undergo partial absorption and partial reflection. When a large amount of melanin is present in the corium, these red rays are more completely absorbed and the blues thus predominate. Jeghers [12] has recently reviewed this subject in detail.

Cardiac Metastases

In regard to cardiac metastases from malignant melanoma, Moragues [13] reviewed the literature in 1939 and noted only 23 reported cases, plus four of his own. Scott and Garvin [14] reviewed a series of 1082 autopsies at the Cleveland City Hospital, 10.9 per cent of which, or 118, showed heart metastases. There were 10 melanomas in this group, five of which metastasized to the heart. Among the cases studied by Moragues at the St. Louis University Hospitals were seven melanomas, four of which developed cardiac metastases. It would therefore appear that melanomas frequently metastasize to the heart. However, massive pericardial effusion secondary to these cardiac metastases is of infrequent occurrence.

The patient described here probably had a small pericardial effusion which was not detected when he first entered the hospital. As the fluid increased, signs of increasing cardiac size and tamponade became evident. Despite tapping, the effusion rapidly reaccumulated. The first fluid withdrawn was a clear, brownish-tinged fluid with the characteristics of a transudate, although of malignant etiology. The fluid subsequently became more sanguinous in nature;

coincidentally, a sanguinous pleural effusion also developed. Hydropneumopericardium was induced to delineate the pericardium, as described by Fenichel and Epstein.[15]

The massive intracardiac and myocardial metastases were striking. Moragues [13] has described a case with a comparable degree of involvement in which a tumor thrombus extended from the right ventricle into the pulmonary conus, almost occluding it. Scott and Garvin [14] mention a case of melanosarcoma of the eye with metastases to the left atrium, left ventricle and pulmonary conus who showed attacks of paroxysmal auricular fibrillation. In the present instance, despite the huge tumor thrombus in the right auricle, there was no clinical or postmortem evidence of blockage of the orifices of the great veins. However, the tricuspid valve was almost occluded. The electrocardiographic changes and clinical findings were principally those associated with pericardial effusion.

Melanuria

Eppinger [16] in 1910 postulated that melanin appears in the urine only when the liver has been extensively involved by melanotic metastases so that a functional insufficiency exists. Blackberg and Wanger [5] stated that melanuria is not noted unless metastases to the liver are present. However, in view of more sensitive concentration methods for detecting minimal amounts of melanin,[4] it is evident this premise must be reëxamined. Moreover, melanuria has been reported in a great variety of conditions.[2, 17, 18, 19] There is no convincing evidence that melanuria is necessarily associated with impaired liver function. In the present study there was evidence of moderate liver damage. However, it is more probable that melanuria occurs when a threshold concentration of melanin bodies is exceeded in the body.[4]

Most of the usual clinical tests for melanuria depend upon the oxidation of a water-soluble colorless or light-colored precursor of melanin, melanogen, to melanin, in the form of a dark brownish-black precipitate. In far-advanced cases, the urine may be dark on passage and become still darker on standing.[20] This was true in the present instance. Melanin pigment may be deposited directly into the kidney tubules if the kidney itself is involved by tumor. Melanin in the urine must be differentiated from bile pigments, blood pigments such as methemoglobin, porphyrins, phenol oxidation products, and alkaptone bodies.[2] The latter may occur in the urine, together with melanin, as in the case reported by Swirsky.[18]

The reagents most often employed in testing for melanin are ferric chloride and bromine water. However, as Rothman,[4] who has studied this subject critically, and others [5] have pointed out, these tests are neither sensitive nor specific, and may yield confusing results in less obvious cases. Moreover, these are little more sensitive than simple darkening of the urine exposed to air. Rothman has found the Thormählen reaction much more satisfactory in that it is highly specific and about 50 times as sensitive as the oxidation tests. Ehrlich's aldehyde reaction is about twice as sensitive as the Thormählen reaction, but less specific for melanin.

The total amount of melanin excreted by this patient per 24 hours, as estimated by the method of Blackberg and Wanger,[5] was noted to be 0.43 gm. and 0.47 gm. on two successive days. This compares with a value of about 1 gm. in three days reported by Peters for a case of melanuria without melanosarcoma.

This is also about the total estimated amount of pigment found in the skin and hair of a dark Negro,[16] indicating the large amount of pigment which may be formed by the body under pathological conditions.

SUMMARY

1. A case of malignant melanoma manifesting diffuse melanosis of the skin, cardiac metastases, pericardial effusion, and melanuria is reported.

2. Diffuse melanosis associated with melanoma may be related to concomitant destruction of the adrenals, as noted in this case.

3. Cardiac metastases are frequently encountered secondary to malignant melanoma. Massive pericardial effusion may also supervene.

4. The pathogenesis and some of the clinical tests for melanuria are discussed; Thormählen's reaction is most satisfactory.

Grateful acknowledgment is made to Dr. C. G. Burn, Director of Pathology, Kings County Hospital, for assistance in preparing this manuscript.

BIBLIOGRAPHY

1. SHINOWARA, G. Y., JONES, L. M., and REINHART, H. L.: The estimation of serum inorganic phosphate and "acid alkaline" phosphatase activity, Jr. Biol. Chem., 1942, cxlii, 921–933.
2. HADEN, R. L., and ORR, T. G.: Melanuria in the absence of melanotic tumor, Bull. Johns Hopkins Hosp., 1924, xxxv, 58.
3. THORMÄHLEN, J.: Mitteilung über einen noch nicht bekannten Korper im pathologischen Menschenharn, Virchow's Arch. f. path. Anat., 1887, cviii, 17.
4. ROTHMAN, STEPHEN: Studies on melanuria, Jr. Lab. and Clin. Med., 1942, xxvii, 637–692.
5. BLACKBERG, S. N., and WANGER, J. O.: Melanuria, Jr. Am. Med. Assoc., 1933, c, 334.
6. WAY, S. C., and LIGHT, S. E.: Generalized melanosis, Jr. Am. Med. Assoc., 1930, xciv, 241–245.
7. ODEL, H. M., MONTGOMERY, H., and HORTON, B. T.: Diffuse melanosis, Proc. Staff Meet. Mayo Clin., 1937, xii, 742–747.
8. DIXON, H. A.: Melanotic sarcoma with extreme melanosis, Arch. Dermat. and Syph., 1938, xxxviii, 574–582.
9. KNISELEY, R. M., and BAGGENSTOSS, A. H.: Primary melanoma of the adrenal gland, Arch. Path., 1946, xlii, 345–349.
10. SOFFER, L. J.: Diseases of the Adrenals, 1946, Lea and Febiger, Philadelphia, pp. 35, 98.
11. EDWARDS, E. A., and DUNTLEY, S. Q.: Pigments and color of living human skin, Am. Jr. Anat., 1939, lxv, 1–33.
12. JEGHERS, H.: Pigmentation of the skin, New England Jr. Med., 1944, ccxxxi, 88–99.
13. MORAGUES, V.: Cardiac metastases from malignant melanoma, Am. Heart Jr., 1939, xviii, 579–588.
14. SCOTT, R. W., and GARVIN, C. F.: Tumors of the heart and pericardium, Am. Heart Jr., 1939, xvii, 431–436.
15. FENICHEL, N. M., and EPSTEIN, B. S.: The clinical and roentgenological diagnosis of pericardial effusion, Ann. Int. Med., 1946, xxiv, 401–412.
16. EPPINGER, H.: Ueber Melanurie, Biochem. Ztschr., 1910, xxviii, 181.
17. PETERS, J. P.: Melanuria without melanosarcoma, Arch. Int. Med., 1923, xxxii, 709.
18. SWIRSKY, M. Y.: Ochronosis. Report of a case with alkaptonuria and melanuria, Clinics, 1944, ii, 1323–1333.
19. LOCKET, S.: Syndrome resembling Addison's disease with melanuria, Brit. Med. Jr., 1945, ii, 417–419.
20. EWING, J.: Neoplastic diseases, 1940, W. B. Saunders Company, Philadelphia, p. 959.

TRANSIENT RIGHT BUNDLE BRANCH BLOCK, WIDE S WAVE TYPE, IN WHICH NORMAL CONDUCTION OCCURRED BOTH SPONTANEOUSLY AND IN RESPONSE TO VAGAL STIMULATION *

By EDWARD NICHOLS,† M.D., *Hartford, Connecticut*

IN routine electrocardiograms taken on healthy young adults without clinical evidence of heart disease, bundle branch block is a rare finding, occurring in less than 1 per cent.[1, 2, 3, 4] Apart from those cases falling into the special class described by Wolff, Parkinson and White, transient bundle branch block has been reported, with rare exceptions,[5] only in association with obvious heart disease clinically or in individuals in whom the age factor alone suggested the likely possibility of coronary sclerosis.[6, 7, 8] The presence of bundle branch block in a 28 year old soldier with a normal cardiovascular system clinically suggested the possible influence of primarily physiological factors. It was found that transient periods of normal conduction occurred on several occasions in response to stimuli considered to act through vagal centers. Spontaneous reversion to normal conduction was noted only once. It is of some interest that attention has been called to the fact that this type of bundle branch block is less often associated wih serious heart disease.[9, 10]

CASE REPORT

C. J. D., a 28 year old infantryman, was admitted to an Army General Hospital on June 1, 1945. His family history was negative, his birth had been normal, and his general health during infancy and childhood was apparently excellent. At the age of 11, because of a sore throat and rash he was admitted to the Charles V. Chapin Hospital in Providence, Rhode Island. While under observation for a period of four weeks no signs suggesting rheumatic fever or diphtheria or any evidence of cardiac dysfunction were noted in the hospital record. Other childhood diseases were denied. He remained in excellent health through four years of college and one additional year at a Catholic University prior to induction into the U. S. Army in July 1942. Basic infantry training was completed without any physical difficulties or complaints and in December 1942 he was ordered to an Officers Candidate School, but "washed out" after eight weeks for non-medical reasons. He continued in good health and in February 1944 went overseas. In June 1944 he first noticed the onset of fleeting arthralgias in the left great toe, left knee, metacarpal phalangeal and interphalangeal joints of the left hand. Concomitantly he developed a chronic head cold without sore throat or fever but accompanied by moderate mucopurulent nasal and postnasal discharge, and a cough productive of small amounts of purulent sputum in the morning which was blood streaked on one occasion. For this he was admitted to an Army General Hospital and observed for three weeks. At no time was he febrile, nor were the joint pains ever accompanied by objective signs. His "sinuses were washed out once" and "special roentgen-rays" (apparently bronchograms) taken prior to discharge to duty. By that time the respiratory symptoms had subsided, and except for mild arthralgias localized as described above, occurring at irregular intervals, he felt well and remained so through the rest of the summer. In December 1944 he was transferred to France for further combat infantry training. The arthralgias subsided at this time except for very occasional mild pains in the left knee. In March 1945

* Received for publication January 3, 1946.
† Previously Major, M.C., A.U.S.

just before going into combat he developed an acute psychosis and was returned to another Army General Hospital for treatment. Upon his arrival there his physical examination was negative and his general condition, except for his mental state, was good. In the course of obtaining medical clearance for insulin shock therapy a routine electrocardiogram was obtained. Both the one taken on April 25 and a repeat tracing on April 26 recorded persistent right bundle branch block. The cardiac examination was otherwise negative. In view of this finding shock treatment was considered inadvisable.

He was evacuated to the United States and admitted to an Army General Hospital on June 1, 1945, as a closed ward patient. Within two weeks his psychiatric condition had improved considerably and he was soon transferred to an open ward. His physical condition continued excellent. He ate well and was afebrile. The system review throughout the time of his admission was negative except for an occasional "sticking pain" located below and outside the cardiac apex. This pain was described as "coming on like a shot and going as fast." It occurred about once a week and more frequently at rest than when active. He admitted having first felt this pain while at Officers Candidate School in 1942, more frequently after arriving in England in 1944, and less often since then. This complaint had never interfered with his activity. There were no other cardiac symptoms. The patient neither drank nor smoked. He remained under observation and treatment until October 4, 1945.

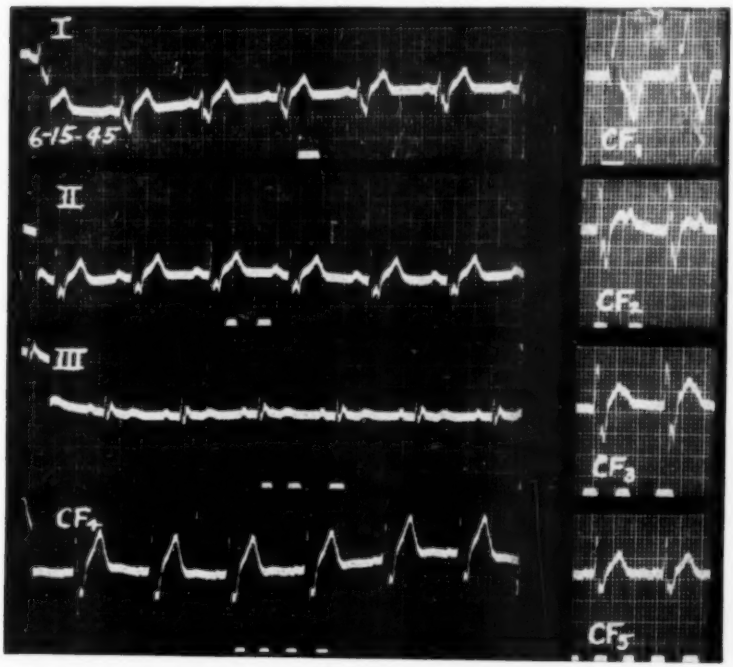


FIG. 1. Routine electrocardiogram taken on June 15, 1945. Right bundle branch block with a wide S wave pattern. Rate 83. P–R interval .13 sec. I–V conduction time, .11 to .12 sec.

Physical Examination. The patient was a quiet, passive, emotionally immature young man appearing younger than his stated age. He was of medium height and build. The general physical examination was not remarkable. The eye grounds were normal. The tonsils were small and not inflamed. There was no evidence of an active sinus infection. The lungs were clear and the abdomen was negative. The extremities were normal and the radial, posterior tibial, and dorsalis pedis vessels were soft with good and equal pulsations bilaterally. There was no evidence of unusual vasomotor activity. The pulse rate was 79 and the rhythm was regular. The blood pressure was 110 mm. Hg systolic and 78 mm. diastolic. The point of maximum impulse was in the fourth interspace 2 cm. inside the nipple line. The heart sounds were not remarkable and there was no splitting or reduplication of the first sound at the apex. In the supine position there was a soft grade 1 blowing systolic murmur audible at the apex but heard more easily in the third left interspace 2 cm. to the left of the sternal border. It disappeared when the patient assumed the sitting or standing position. The murmur was not transmitted to the axilla or lung bases posteriorly. After running in place for one minute (approximately 187 steps) the heart rate increased from 79 to 140 per minute and the respiratory rate from 16 to 28 per minute. Following cessation of effort the heart rate noted at one, two, three and five minute intervals was 110, 100, 94, and 82 respectively. The patient did not complain of dyspnea, palpitation or cardiac pain. No change was noted in the quality or intensity of the systolic murmur.

Laboratory Data. The complete blood count and urine examinations were not remarkable. The stool was negative for ova and parasites. The Kahn reaction was negative. Repeated erythrocyte sedimentation rates (Wintrobe) were all below 8 mm. per hour. Blood chemistry findings included the following: Non-protein nitrogen 30 mg. per cent, fasting blood sugar 91 mg. per cent, cholesterol 165 mg. per cent, phosphorus 3.5 mg. per cent, calcium 10.5 mg. per cent, and serum proteins 6 gm. per cent with an A/G ratio of 1.5/1. A roentgenogram of the chest was negative. A teleroentgenogram showed the heart to be small but within normal limits according to the Ungerleider tables. Fluoroscopy of the heart with barium swallow revealed no abnor-

TABLE I

Showing the Dates on Which Observations Were Made and the Effect of Various Procedures on Intraventricular Conduction

Date	6-18/45	6-28/45	7-15/45	7-20/45	8-6/45	8-15/45	8-20/45	8-27/45	9-12/45
Control period	0	X	0	0	0	0	0	0	0
Controlled breathing alone		X	0	0	0	0	0	0	0
Changes in position			0	0	0				0
Carotid sinus stimulation			X	0	0	0	0		
Atropine early effect 10–15 min.	X	X	X				0*		X
Atropine late effect after 30 min.	0	0	0				0		0
Oxygen						0			
Amyl nitrite						0			
Ergotamine					0				
Prostigmine								0	

0—No change, persistent right bundle branch block.
X—Periods of transient reversion to normal I–V conduction noted.
*—On this occasion the dose of atropine was increased to 2.5 mg.

malities of the heart, lungs or great vessels. An electrocardiogram taken on June 15, 1945 recorded right bundle branch block with a wide S wave pattern. The P–R interval was .13 to .14 second and the interventricular conduction time .11 to .12 second (figure 1). Although the history raised the possibility of an episode of rheumatic fever in the past it was the opinion of the author that the evidence for this diagnosis was insufficient. The possibility of the murmur being related to a congenital lesion was also considered but as the murmur fulfilled the usually accepted criteria of a "physiological murmur" and the rest of the examination was negative this diagnosis also seemed unwarranted.

Course. During the four months of the patient's admission his electrocardiogram was followed at length on nine occasions (table 1). On each, prior to observing the effect of a drug, any maneuver or series of maneuvers, Lead II was observed for 20 to 30 minutes with the patient resting in the supine position to establish a base line. All tracings illustrated were taken with the subject supine. Changes in position, where noted, include approximately five minutes of observation in the right and left

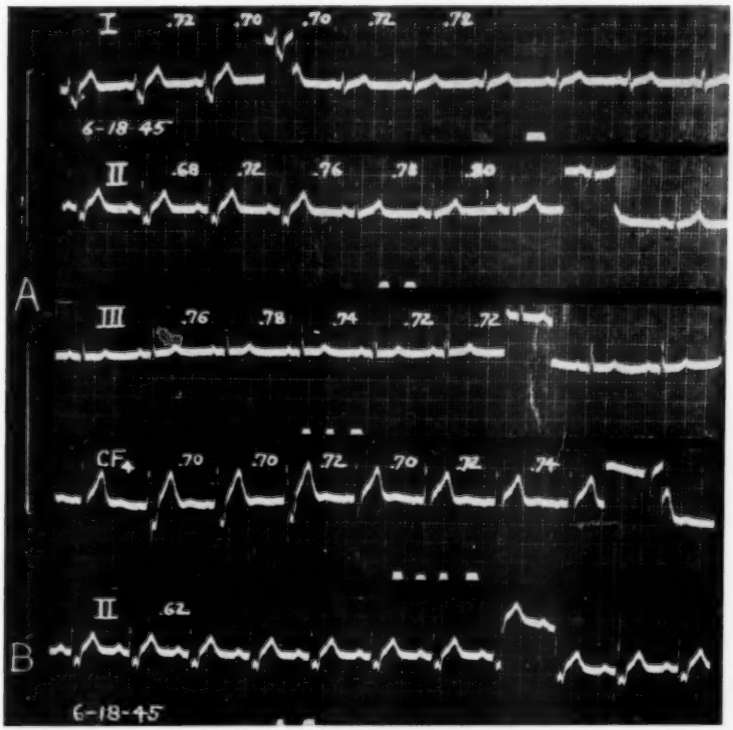


FIG. 2. *A*, June 18, 1945. Electrocardiogram taken 15 minutes after the subcutaneous injection of 1.5 mg. of atropine sulfate showing transitions from right bundle branch block to normal conduction in all leads but III. *B*, a portion of Lead II taken 15 minutes after *A* showing persistent right bundle branch block. Time intervals between complexes where noted are in tenths of seconds.

lateral, sitting and standing positions. After the vagal effect of controlled breathing was first observed on June 28 it was used subsequently when studying the effect of each drug or maneuver with the thought that it might reinforce any tendency to change. In each instance the patient was directed to take a maximum breath quickly, hold it for a moment, then expire naturally not forcibly.

The various occasions on which observations were made are not described in chronological order as listed in table 1, but are grouped otherwise for brevity and simplification.

The response to atropine sulfate was observed on four occasions. On three of these during the eight to 15 minute period following the subcutaneous injection of 1.5 mg. of the drug abrupt transitions from right bundle branch block to normal conduction for variable periods were recorded (figures 2 and 3). The intervals of normal conduction covered a single or multiple complexes. The largest number of successive normal complexes recorded was 34. When a tendency to sinus arrhythmia was present and particularly when it was enhanced by controlled breathing during the eight to 15 minute interval, transition to normal conduction occurred with the onset of expiratory slowing and lasted until the next inspiration began (figure 3 c, d, and e).

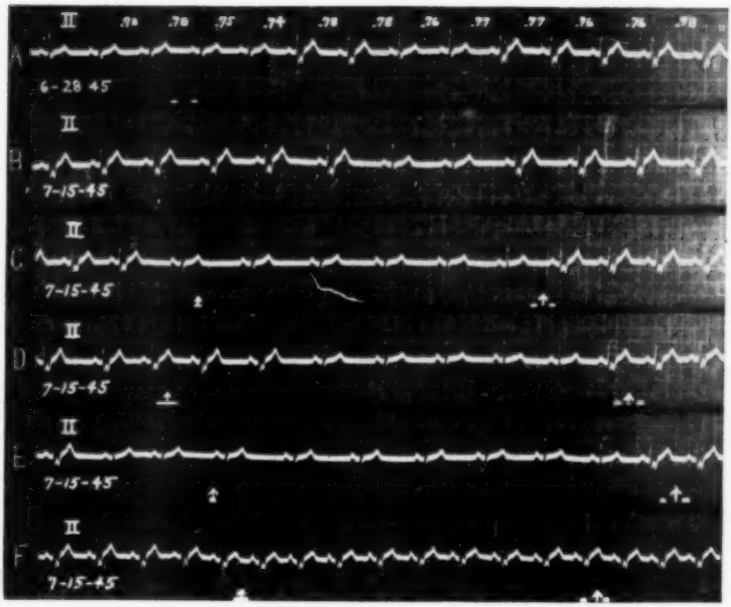


FIG. 3. *A*, June 28, 1945. Sample of Lead II taken during the 30 minute control period showing spontaneous transitions to normal conduction. *B*, August 15, 1945. One of two pairs of normal complexes occurring during left carotid sinus stimulation. *C*, *D*, and *E*, July 15, 1945. The effect of three successive breaths during controlled breathing observed in the 10 to 15 minute period following 1.5 mg. of atropine. One tap on the lead indicator marks the height of inspiration and two taps the end of the succeeding expiration. *F*, a portion of Lead II taken 15 minutes after *C*, *D*, and *E*, recording the increase in rate, disappearance of the response to controlled breathing and return of persistent bundle branch block. Time intervals between complexes where noted are in tenths of seconds.

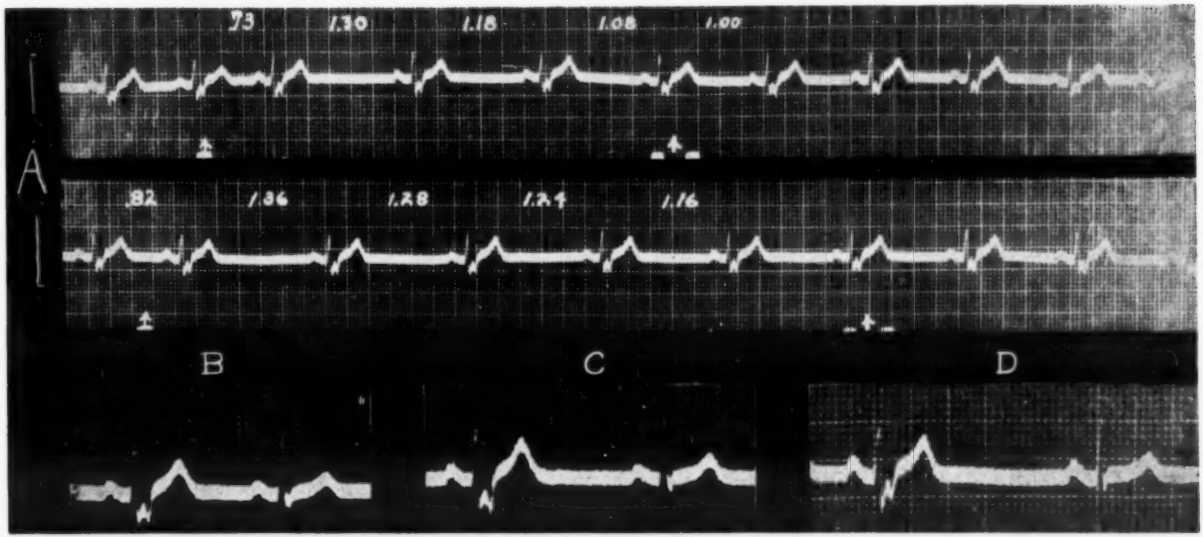


FIG. 4. *A*, August 6, 1945. Samples of Lead II during two successive breaths 30 minutes after the subcutaneous injection of 0.5 mg. of ergotamine tartrate recording a marked sinus arrhythmia in response to controlled breathing and persistent right bundle branch block. *B*, *C*, and *D*, magnifications of the recorded abrupt reversion to normal conduction as it occurred, *B*, spontaneously on June 28, 1945, *C*, during left carotid sinus stimulation on July 15, 1945, and *D*, during the 10 to 15 minute period following atropine on September 12, 1945. Time intervals where noted are in tenths of seconds.

Although reversion to normal conduction could be regulated during this period by controlled breathing this maneuver was not necessary for transition to occur. Reversion otherwise was unpredictable and did occur without any significant change in rate as recorded in Leads I and 4F of figure 2. Eighteen minutes after the injection no normal complexes were noted on any occasion. At this point the parasympatheticolytic effect of atropine became evident, the rate increased to between 90 and 100, and the response to controlled breathing disappeared (figure 2).

On one occasion when the dose of atropine was increased to 2.5 mg. (August 20, 1945), transition to normal conduction was not noted during the eight to 15 minute period following the injection.* Although very slight slowing was observed during the expiratory phase of controlled breathing it was transient and soon followed by a persistent tachycardia.

Spontaneous reversion to normal conduction was observed only once on June 28 (figure 3*a*). The number of successive normal complexes varied from one to 17. These occurred throughout the control period, tending neither to increase nor decrease. No significant sinus arrhythmia was present and the occurrence of normal or blocked complexes bore no definite relation to what slight variations in rate existed. The subcutaneous injection of 1.5 mg. of atropine sulfate was not followed by an increase in the number of normal complexes during the eight to 15 minute period following the drug. It was first noted on this occasion that transient reversion to normal conduction could be regulated by controlled breathing. After 20 minutes the parasympatheticolytic effect of atropine was evidenced by a fixed rapid rate and normal complexes were no longer observed.

The effect of pressure on the left, right and both carotid sinuses in the standing and supine positions was observed on four different occasions. Transition to normal conduction was noted only once (figure 3*b*), during left carotid sinus pressure, and consisted of two pairs of normal complexes.

Changes in position observed on four occasions, the administration of 100 per cent oxygen through a BLB mask for five minutes, the intramuscular injection of 2.5 mg. of prostigmine and the inhalation of amyl nitrite (0.32 c.c.), each observed on one occasion, had no effect on the bundle branch block.

Although the intramuscular injection of 0.5 mg. of ergotamine tartrate resulted in the most marked sinus arrhythmia in response to controlled breathing, no effect on the bundle branch block was noted (figure 4).

Discussion

It is generally accepted that bundle branch block can occur in the absence of a demonstrable histological lesion. Transient bundle branch block has been reported in congenital heart disease, and associated with diphtheritic myocarditis, chronic rheumatic heart disease with and without active rheumatic infection, thyrotoxicosis, hypertension and arteriosclerosis, and with coronary sclerosis with and without myocardial infarction. In these instances a degree of temporary impairment in the metabolism of that part of the bundle branch system which would depress conduction sufficiently to produce the particular effect was generally hypothesized as the most reasonable explanation of the phenomenon. Transient bundle branch block has also been reported during quinidine adminis-

* It is generally accepted [24, 25] that small doses of atropine stimulate and do not paralyze the vagus. The dosage level above which paralysis can generally be expected to occur is about 2.0 mg. Dosages of 2.5 mg. have been noted, however, to be followed by short periods of vagal stimulation before the effects of paralysis became evident.[13] It is apparent that not only the size of the dose but also the time of action as well as the subject's individual tolerance must be taken into consideration before evaluating the effect of a given dose.

tration in the treatment of heart disease. In general, conduction was observed to improve or return to normal with improvement in the cardiac status. The fact that pathological processes are not necessarily permanent and that abnormal physiological states may precede eventual pathologic responses has been emphasized as an important consideration in evaluating the significance of transient bundle branch block, and is supported by clear cut evidence of cardiac disease in all but an exceptional case.[6] In certain instances, however, one is led more forcibly to seek other possible explanations. Although underlying pathologic lesions cannot be ruled out in the case presented here, there is nothing save the conduction abnormality to suggest their presence. "Fatigue" of a pathologically depressed bundle branch, if it cannot be eliminated as a contributing factor, would hardly seem to be of much significance. None of the factors potentiating myocardial fatigue were present and normal conduction was observed to occur transiently without any change in rate both spontaneously and during the period of early atropine effect. It also was not observed when the slowest rates noted were induced by controlled breathing following ergotamine.

More interest has been directed recently to the effects of postural and respiratory maneuvers, carotid sinus stimulation, and various autonomic drugs on certain phases of cardiac conduction.[4, 11, 12, 13, and 14] Technics employing these effects have been utilized in evaluating the significance of abnormalities in A-V conduction and the form, amplitude and polarity of T-waves in both the limb and chest leads.[13, 14, and 16] The importance of autonomic controls as contributing influences on these phases of the electrocardiographic pattern in certain individuals has been convincingly demonstrated.

Various factors, chemical, mechanical and nervous, contributing to the development of transient bundle branch block, have been suggested, and attention has been repeatedly called to the influence of indirect vagal effects.[6, 7, 8, 17, and 18] Although experimentally stimulation of the vagus has been shown to affect intraventricular conduction,[19] clinical evidence of this is not clear and in those cases in which vagal influence is suggested it seems impossible to determine just what may represent a direct effect or manifest an indirect response to other vagal actions, principally slowing of the heart rate. Until the Wolff-Parkinson-White syndrome is completely understood the action of atropine in those instances in which the conduction mechanism is affected by the drug will remain in doubt. Recent histological studies have raised again a question in the minds of certain investigators as to the existence of a sufficiently distinct anatomical structure in the human heart to warrant the name of a bundle branch system.[20] In view of conflicting studies and opinions on this point in the accumulated literature of the past it would seem reasonable to assume that the question was still open. Irrespective of the anatomical factors involved certain experimental evidence related to the effect of atropine on conduction in the intact mammalian heart appeared to throw some light on the apparent early vagal action of atropine on intraventricular conduction in the case presented here.

The effects of atropine on conduction in auricular, ventricular and A-V nodal tissue of the mammalian heart under very high rates of stimulation have been studied at length.[21] Under these conditions, when doses of atropine sufficient to paralyze the vagus are given, the refractory period in all three types of tissue is prolonged leading to varying degrees of block. The refractory period of A-V nodal tissue is similarly influenced by section of both vagi. Conversely it

has been demonstrated in the case of auricular muscle under very high rates of stimulation that increased vagal tone decreases the refractory period.[22] In general, however, the effect of vagal stimulation on the A-V node is to prolong conduction time through the node and produce varying degrees of A-V block. It has been pointed out that any concept of the action of the vagus on the heart must explain these apparently paradoxical effects and an hypothesis based on a dual action of the vagus has been suggested.[23] According to this concept vagal stimulation not only shortens the refractory period but also decreases the rate at which excitability returns, and this latter effect on the A-V node which has a longer refractory period and presumably slower metabolic processes is more marked and the determining vagal influence on conduction through the A-V node. In applying this concept to the interpretation of certain experimental results where vagal stimulation has decreased the degree of A-V block it has been suggested that under certain conditions the generally negligible effect on the refractory period becomes the one of primary influence.[23] Instances in which vagal stimulation clinically have shortened rather than prolonged A-V conduction have been reported.[23] It does not seem unreasonable to assume that a similar state of affairs may exist in the conduction pathways from the node to the ventricles and that conduction along these pathways is subject to similar influences.

In this case the early parasympathomimetic effect of atropine did not affect the P-R interval but was associated with periods of transient normal intraventricular conduction. One is led to consider the possibility of vagal action on the conduction mechanism other than a decrease in heart rate and immediately related effects, and that this reversion to normal conduction might result from a transient decrease in the refractory period of the abnormally functioning part of the conduction pathway leading to the right ventricle.

Summary

A case of right bundle branch block with a wide S-wave pattern occurring in a 28 year old soldier without other evidence of heart disease is presented. Transient periods of normal conduction were observed to occur once spontaneously, once during stimulation of the left carotid sinus and on three occasions during the early period of parasympathomimetic action following the subcutaneous injection of 1.5 mg. of atropine. The phenomenon is briefly discussed.

BIBLIOGRAPHY

1. Ferguson, D., and O'Connell, J. T.: Cardiovascular observations, U. S. Med. Bull., 1926, xxiv, 860.
2. Wood, F. C., Wolferth, C. C., and Miller, T. G.: Electrocardiography in military medicine, War Med., 1941, i, 696.
3. Hall, G. C., Steward, C. B., and Manning, C. W.: The electrocardiographic records of 2000 R. C. A. F. Aircrew, Canad. Med. Assoc. Jr., 1942, xlvi, 226.
4. Thomas, C. B.: The significance of electrocardiographic abnormalities in young adults, Bull. Johns Hopkins Hosp., 1944, lxxix, 229.
5. Eichert, H.: Transient bundle branch block associated with tachycardia, Am. Heart Jr., 1944, xxviii, 551.
6. Sigler, L. H.: Functional bundle branch block, Am. Jr. Med. Sci., 1944, cxxcv, 211.
7. Yater, W. M.: Pathogenesis of bundle branch block, Arch. Int. Med., 1938, lxii, 1.

8. Comeau, W. J., Hamilton, J., and White, P. D.: Paroxysmal bundle branch block associated with heart disease, Am. Heart Jr., 1938, xv, 276.
9. Wood, F. C., Jeffers, W. A., and Wolferth, C. C.: Follow-up study of 64 patients with a right bundle branch block conduction defect, Am. Heart Jr., 1935, x, 1056.
10. Willius, F. A., Dry, T. J., and Resser, R., Jr.: Life expectancy in conductive disturbances affecting the ventricular complex of the electrocardiogram, general considerations of bundle branch block with concordant and with discordant graphs and the wide S wave pattern, based on 1611 cases, Arch. Int. Med., 1941, lxvii, 1008.
11. Holmes, J. H., and Laque, R. B.: Incomplete heart block produced by changes in posture, Am. Heart Jr., 1945, xxx, 3.
12. Manning, G. W., and Stewart, C. B.: Alteration from normal to abnormal P–R interval with change in posture, Canad. Med. Assoc. Jr., 1944, li, 546.
13. Wendkos, M. H.: The influence of autonomic imbalance on the human electrocardiogram. 1. Unstable T waves in precordial leads from emotionally unstable persons without organic heart disease, Am. Heart Jr., 1944, xxviii, 549.
14. White, P. D., Chamberlain, L., and Graybiel, A.: Inversion of the T waves in lead 2 caused by variations in position of the heart, Brit. Heart Jr., 1941, iii, 233.
15. Wendkos, M. H., and Laque, R. B.: Unstable T waves in leads 2 and 3 in persons with neurocirculatory asthenia, Am. Heart Jr., 1946, xxxi, 74.
16. Bruenn, J. J.: Mechanism of impaired auriculoventricular conduction in acute rheumatic fever, Am. Heart Jr., 1937, xiii, 413.
17. Wilson, F. N.: A case in which the vagus influenced the form of the ventricular complex of the electrocardiogram, Arch. Int. Med., 1915, xvi, 1008.
18. Hermann, G. R., and Ashman, R.: Partial bundle branch block. Theoretical consideration of transient normal intraventricular conduction in the presence of apparently complete bundle branch block, Am. Heart Jr., 1931, vi, 375.
19. Lewis, T.: The mechanism and graphic registration of the heart beat, 1925, Shaw & Sons, London, p. 169.
20. Glomset, D. J., Glomset, A. T. A., and Birge, R. F.: Morphologic study of the cardiac conduction system. Part III: Bundle branch block, Am. Heart Jr., 1944, xxviii, 348.
21. Lewis, T., Drury, A. N., and Iliescu, C. C.: Some observations on atropine and strophanthin, Heart, 1921, ix, 21.
22. Lewis, T., Drury, A. N., and Bulger, H. A.: Observations on flutter and fibrillation. Part 2. The refractory period and rate of propagation in the auricle: Their relation to block in the auricular walls and to flutter, etc., Heart, 1921, viii, 83.
23. Lewis, T.: The law of cardiac muscle with special reference to conduction in the mammalian heart, Quart. Jr. Med., 1921, xiv, 339.
24. Solomon's Pharmacology, 6th Edit., 1942, W. B. Saunders, Philadelphia, page 371.
25. Goodman, M. A., and Gilman, A.: The Pharmacological Basis of Therapeutics, 1941, Macmillan, New York, p. 465.

MEDIASTINAL EMPHYSEMA FOLLOWING ANTERIOR PERFORATION OF A GASTRIC ULCER*

By Dalton M. Welty, Captain, M.C., A.U.S., *Hot Springs, South Dakota*

During the past 20 years mediastinal emphysema has been recognized with increasing frequency and a large number of papers are now available in the medi-

* Received for publication May 21, 1946.
From the Medical Service of the United States Veterans Hospital, Hot Springs, South Dakota.

cal literature bearing on its pathologic physiology and clinical manifestations.[1, 2, 3, 4, 5] McGuire and Bean [6] have credited Laennec with the original description of the peculiar bubbling, crackling and popping sounds now considered so characteristic. Müller,[7] in 1888, described bubbling crepitations synchronous with the heart beat as indicative of pneumomediastinum.

Mediastinal emphysema is most often a complication of another disease or condition. Air can reach the mediastinum from perforation of the esophagus, trachea or bronchus. It may extend to the mediastinum from a collection of air introduced into the fascial planes of the neck or from a collection of air in the retroperitoneum. For years it was assumed that air frequently entered the mediastinum from a ruptured emphysematous bleb, although this rarely if ever has been confirmed at post mortem. Macklin,[8, 9] in a series of experiments on cats and other animals, has clarified the mechanism of what is probably the most common cause of mediastinal emphysema, namely interstitial emphysema of the lungs. He has been able to show that under increased intra-pulmonary pressure the air may enter the perivascular sheaths of the finer branches of the pulmonary vessels and move along these sheaths toward the root of the lung. Some of this air may go peripherally but apparently most of it collects in the hilar region as a result of pressure gradients and finally bursts through into the mediastinum. This sequence of events is more likely to occur when partial bronchial obstruction exists to produce distention and easier rupture of alveoli. Alveolar rupture is thought to be truly spontaneous at times when no definite condition tending to increase intra-alveolar pressure is found. Hamman,[10, 11, 12] more than any other, has directed our attention to this condition and correlated our knowledge in a comprehensive manner.

The purpose of this communication is to present an instance of mediastinal emphysema apparently arising secondary to pneumoperitoneum following perforation of a gastric ulcer. The mediastinal emphysema was a confusing aspect of the clinical picture.

Case Report

H. B., a 58 year old single man, a laborer and plasterer by occupation, was admitted to the United States Veterans Hospital at Hot Springs, South Dakota for the fifth time on September 5, 1945. The admissions over a four year period had been for treatment of carcinoma of the tongue with extension into the mandible. This tumor had been treated first with radium and then by excision of the anterior two-thirds of his tongue in August 1942. In his last admission it was not certain whether he had a local extension of malignancy into the mandible or whether the bone was involved in irradiation necrosis. Roentgenogram of the chest showed no metastasis and very slight increase in the broncho-vascular markings. The patient had no gastrointestinal complaints until just after the evening meal on January 9, 1946 when he developed quite suddenly a severe steady upper abdominal pain. When seen in medical consultation the following morning examination disclosed temperature 103.8° (rectally), pulse 116, respirations 28, blood pressure 90 mm. Hg systolic and 60 mm. diastolic. The patient was an elderly man appearing acutely ill, cyanotic and apprehensive with upper abdominal and lower anterior chest pain. There was no icterus of skin or sclera. The stump of the tongue and the pharynx appeared dry. A small ulceration was present on the inner aspect of the left mandible. The left anterior cervical nodes were marble-sized and quite firm. The trachea was in the mid-line. The thyroid gland was not palpable. The neck veins were moderately distended with

patient in the semi-recumbent position. There was no evidence of subcutaneous emphysema. The anterior-posterior diameter of the chest was slightly increased and the subcostal angle obtuse but otherwise the lungs were clear. The heart borders could not be outlined and the point of maximal impulse could not be seen or felt. A peculiar grating sensation was palpable over the precordium at the level of the third, fourth and fifth interspaces to the left of the sternum. On auscultation over the precordium the cardiac tones were obscured by loud crackling, crunching and popping sounds accentuated by deep inspiration. The sounds continued, however, even in absence of respiration and were alternately louder and fainter depending on the phase of the cardiac cycle. The upper abdomen was markedly rigid and tender on pressure. The liver, spleen and kidneys could not be felt. There were no masses or herniae. The lateral lobes of the prostate gland showed moderate firm enlargement, otherwise the rectal examination was negative. The white blood cell count was 26,850 with 96 per cent polymorphonuclears and 4 per cent lymphocytes; red blood cells 5,600,000; hemoglobin 90 per cent. The urine was within normal limits. Wassermann and Kahn reactions were negative.

The question immediately arose as to whether acute mediastinal emphysema could explain all of his symptoms or whether the mediastinal emphysema was secondary to a perforated abdominal viscus. Because of the critical condition of the patient it was difficult to carry out adequate roentgenologic examinations. Portable anterior posterior roentgen-ray of chest showed a high left diaphragm but no definite air in the mediastinum. A satisfactory lateral roentgen-ray of the chest could not be obtained. With the patient tilted at a 45 degree angle a large amount of air was visualized under the dome of the diaphragm. Laparotomy was done and a perforated ulcer was found on the anterior-superior aspect of the lesser curvature of the stomach about two inches above the pylorus. Very little scar tissue was found about the ulcer. Apparently it was an acutely ulcerative process. The ulcer was closed and postoperatively the patient did surprisingly well. The bubbling, crackling and popping sounds gradually diminished in intensity until they disappeared altogether on the fourth post-operative day. The heart sounds then were heard normally, were regular, of good quality and without murmurs. Three weeks later when the patient had apparently completely recovered from the acute episode he had a sudden massive hemorrhage from the left mandible and died as a result of this. Postmortem examination was denied us.

Discussion

It is not clear how air can reach the mediastinum from a collection of intraperitoneal air when the parietal peritoneum has not been injured. Both the lesser and greater peritoneal cavities are closed spaces. It is easy to see how air in the retroperitoneum can gain access to the mediastinum through the aortic, esophageal or vena caval hiatuses or conversely how mediastinal air can extend to produce pneumo-retroperitoneum as in Adcock's case.[13] Perforation of the stomach high in the cardia in the area not covered with peritoneum or perforation of an ulcer on the posterior wall of the duodenum can lead to mediastinal emphysema without first producing pneumoperitoneum. A number of such cases have been reported.[14, 15, 16]

Banyai and Jurgens [17] report seven cases of mediastinal emphysema following artificial pneumoperitoneum. It is significant, however, that in all of these cases the pneumoperitoneum was induced by the subphrenic route. In this method the point of the needle is supposed to be above the costal margin and below the costophrenic reflection of pleura. It would thus be possible for the needle to traumatize the diaphragm, to elevate the basal parietal pleura or to penetrate the lung it-

self. Thus the air could gain access to the mediastinum without having first to traverse the peritoneal cavity. McCorkle and Stevenson [18] report a case in 1937 of perforation of an ulcer on the anterior surface of the duodenum with pneumoperitoneum, mediastinal emphysema and subcutaneous emphysema. In their case no abnormal cardiac signs are mentioned and the anterior-posterior chest roentgenogram reveals no evidence of air in the mediastinum. The authors specifically mention that there was no evidence of posterior perforation of the duodenum.

Two ways in which gas might extend from the peritoneal cavity to the mediastinum to the subcutaneous tissues have been suggested [14, 15]: 1. By direct diffusion through the parietal peritoneum especially when the pneumoperitoneum is extensive and under pressure and when the parietal peritoneum is damaged by inflammatory process. 2. Diffusion of gas from the site of perforation subserously along peritoneally covered ligamentous structures such as the hepatoduodenal or round ligament to the umbilicus or by way of the phrenico-esophageal ligament and aortic hiatus into the mediastinum.

Experimentally in cadavers and dogs Podlaha [16] demonstrated the pathways of extension of gas from the various parts of the stomach and duodenal regions. He injected hydrogen peroxide into the subserous tissues and found that, from injection around the pylorus, the material passed along the hepato-duodenal and round ligament to the umbilical region and that, from injection around the cardia, the material principally followed the phrenico-esophageal ligament and aortic hiatus into the posterior mediastinum.

In view of Macklin's work showing how gas can follow the vascular sheaths of blood vessels a third way is suggested. A subperitoneal collection of gas could enter the perivascular sheaths of the great vessels supplying the region of the perforation and extend eventually to reach the aorta and pass through the aortic hiatus into the mediastinum.

The objection may be raised in my case that the mediastinal emphysema was merely a coincidence and might have been secondary to the carcinoma about the mandible or possibly have had a direct pulmonary cause. Unfortunately no autopsy was obtained to eliminate these possibilities. However, there was no emphysema about the tissues of the neck at any time and this might have been expected were the gas extending from the mandibular region. Its appearance at the time of or shortly after the ulcer perforation and its rapid disappearance following closure of the perforation lead me to feel that the perforation was more than a coincidental event. There was no definite evidence of pulmonary disease.

Summary

Mediastinal emphysema can occur following perforation of a peptic ulcer into the peritoneal cavity. A case is reported and the available literature briefly reviewed. Theoretically the gas could extend to the mediastinum by (*a*) passage along the perivascular sheaths of the great vessels to the aorta and through the aortic hiatus into the mediastinum, (*b*) direct diffusion through the parietal peritoneum, (*c*) passage along the phrenico-esophageal ligament and through the aortic hiatus when the perforation is near the cardia. It is felt most likely that the gas followed the perivascular sheaths of the great blood vessels to reach the mediastinum in this case.

BIBLIOGRAPHY

1. Griffin, R. J.: A diagnostic sign of interstitial emphysema of the mediastinum, Ann. Int. Med., 1942, xvii, 295–297. Spontaneous pneumothorax, Kentucky Med. Jr., 1941, xxxix, 284–288.
2. Greene, J. A.: Unusual sounds emanating from the chest, Arch. Int. Med., 1943, lxxi, 410–414.
3. Miller, H.: Spontaneous mediastinal emphysema, Ann. Int. Med., 1944, xxi, 998–1010. Spontaneous mediastinal emphysema simulating organic heart disease, Am. Jr. Med. Sci., 1945, ccix, 211–220.
4. Iglauer, S.: Spontaneous mediastinal emphysema; case, Ann. Otol., Rhin. and Laryng., 1944, liii, 823–828.
5. Lintz, R. M.: Spontaneous mediastinal emphysema, Ann. Int. Med., 1943, lxxi, 256–261.
6. McGuire, J., and Bean, W. B.: Spontaneous interstitial emphysema of the lungs, Am. Jr. Med. Sci., 1939, cxcvii, 502–509.
7. Müller, F.: Über Emphysem des Mediastinum. Berl. klin. Wchnschr., 1888, xxv, 205–208.
8. Macklin, C. C.: Transport of air along sheaths of pulmonic vessels from alveoli to mediastinum: Clinical implication, Arch. Int. Med., 1939, lxiv, 913–926. Impediment to circulation occasioned by pulmonic interstitial emphysema and pneumo-mediastinum, Jr. Mich. Med. Soc., 1940, xxxix, 756–759.
9. Macklin, M. T., and Macklin, C. C.: Malignant emphysema of lungs and mediastinum as important occult complication in many respiratory diseases and other conditions; interpretation in light of laboratory experiment, Medicine, 1944, xxiii, 281–358. Pulmonic interstitial emphysema and its sequelae; anatomic interpretation, Essay in Biol., 1943, 331–368.
10. Hamman, L.: Spontaneous interstitial emphysema of the lungs, Trans. Assoc. Am. Phys., 1937, lii, 311–319.
11. Hamman, L.: Spontaneous mediastinal emphysema, Bull. Johns Hopkins Hosp., 1939, lxiv, 1–21.
12. Hamman, L.: Mediastinal emphysema, Jr. Am. Med. Assoc., 1945, cxxviii, 1–6.
13. Adcock, J. D.: Spontaneous interstitial emphysema of the lung with mediastinal, retroperitoneal and subcutaneous emphysema, Arch. Int. Med., 1943, 650–657.
14. Korach, S.: Zur Frage des Hautemphysems nach Perforation Gastroduodenaler Geschwüre, Zentralbl. f. Chir., 1927, liv, 1489.
15. Hurst, Arthur F., and Stewart, Mathew J.: Gastric and duodenal ulcer, London, 1929, Oxford University Press, p. 321.
16. Podlaha, Josef: Zur Frage des subkutanen Emphysems bei perforatierten gastroduodenalen Geschwüren, Zentralbl. f. Chir., 1926, 2839.
17. Banyai, A. L., and Jurgens, G. H.: Mediastinal emphysema as a complication of artificial pneumoperitoneum, Jr. Thorac. Surg., 1939, viii, 329–333.
18. McCorkle, H., and Stevenson, J.: Subcutaneous emphysema associated with perforated gastric ulcer, Surgery, 1937, ii, 930–936.

DISSEMINATED LUPUS ERYTHEMATOSUS WITH PERICARDIAL EFFUSION *

By Arthur C. Curtis, M.D., F.A.C.P., and S. F. Horne, M.D.,
Ann Arbor, Michigan

Disseminated lupus erythematosus, although not a common disease, is more frequently recognized than in the past, and as more and more observations are

* Received for publication February 7, 1947.
From the Department of Dermatology and Syphilology of the University of Michigan Medical School.

recorded, it becomes apparent that it represents a syndrome in which there may be varying visceral and cutaneous manifestations. It is essentially a diffuse vascular disease involving the small vessels of the skin and viscera, although recent studies [1] in which fibrinoid degeneration and sclerosis of the collagen are described as the fundamental change in lupus erythematosus indicate that the concept of a diffuse disease of the peripheral circulation can no longer be entertained without question.

Hebra,[2] in 1845, first described lupus erythematosus under the name "seborrhea congestive." Six years later Cazenave [3] gave the disease its present name, but it was not until 1872 that Kaposi [4] subdivided the disease into "lupus erythematosus discoides" and "lupus erythematosus discoides and aggregatus" and pointed out the systemic manifestations of the latter form. Although this early investigator described the clinical picture much as we know it today, several articles published since that time stand out as being particularly valuable in determining the many and varied manifestations of this confusing syndrome. These observations include the erythema group of cutaneous diseases with visceral manifestations described by Sir William Osler in 1895, 1900, and 1904,[5, 6, 7] the atypical verrucous endocarditis recognized by Libman in 1911, and reported more fully by Libman and Sachs in 1924,[8] the polyserositis, polyarthritis and glomerulonephritis with long-continued fever described by Christian in 1935,[9] and a diffuse disease of the peripheral circulation usually associated with lupus erythematosus and endocarditis described by Baehr and associates the same year.[10] The Reifensteins [11] have emphasized the relationship between these manifestations; and the work of Montgomery [12] and Klemperer, et al.[1] has contributed greatly to a better understanding of the fundamental pathological process.

However, despite the varying and often confusing lesions reported in this disease, we have been unable to find a reported case in which a pericardial effusion was the most striking and troublesome manifestation, nor one accompanied by an adhesive pericarditis. Jarcho [13] reports a case in which there was a sacculated pericardial effusion; Fox [14] described a patient in whom a terminal pericardial effusion, 500 c.c., was found at autopsy, and Contratto and Levine's case [15] had 250 c.c. of fluid at postmortem examination, but no previous clinical or roentgenological evidence of pericardial effusion. A patient reported by Blount and Barrett [16] had 100 c.c. of light yellow fluid in the pericardium at autopsy, but the only clinical evidence was an electrocardiogram compatible with such a diagnosis. Numerous authors report that "pericarditis" (without a qualifying diagnosis) is common, but do not mention pericardial effusion per se, whereas Rose and Goldberg [17] state that pericarditis with effusion has been described in detail by various writers, but do not give references. Rakov and Taylor [18] on the other hand, point out that pericarditis with effusion is a rare manifestation of disseminated lupus erythematosus and there are reports of numerous cases [1, 5, 8, 11, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23] in which there is no recorded evidence of a clinical diagnosis of pericardial effusion. Although disseminated lupus erythematosus has been observed by the authors many times, the patients reported here are the only ones in which a pericardial effusion has been recognized clinically.

Case Reports

Case 1. A 23 year old white single female was first admitted to the University Hospital on July 19, 1942, complaining of dyspnea and vomiting. Generalized malaise

and tiredness had been present for 18 months. In February 1942, she developed a migratory polyarthritis with swelling, pain, redness, increased heat and pain on motion in the joints of the wrist, ankles, knees, elbows, shoulders, fingers and toes. She was feverish at the time, but did not consult a physician. After a period of two to three weeks the symptoms subsided spontaneously without residue, only to recur several times during the interval between the onset of her acute symptoms and her admission to the hospital. Since the onset of the joint symptoms she had noted shortness of breath on exertion and one month prior to admission had an attack of paroxysmal nocturnal dyspnea. She had had a daily elevation of temperature as high as 104° F. for four weeks prior to admission. She had lost eight pounds in weight during the illness and had vomited several times the day before admission to the hospital.

Physical Examination: The patient was an acutely ill, well developed and nourished white female. Temperature 103° F., pulse 100, respirations 24, blood pressure 118 mm. Hg systolic and 74 mm. diastolic. There were no skin lesions. The neck veins were slightly engorged. The lungs were clear. There was enlargement of the heart; the point of maximum impulse could not be felt. There was a gallop rhythm and a friction rub was heard just to the left of the sternum in the third and fourth interspaces. There was a paradoxical pulse of 30 mm. of mercury. The liver was palpable four fingers below the right costal margin. The joints were not abnormal, and the remainder of the physical examination was essentially negative.

Laboratory Findings: The hemoglobin varied from 43 to 70 per cent, the red blood count from 2,200,000 to 4,800,000 per cu. mm., and the white blood count from 5300 to 18,800 per cu. mm. The differential count was essentially normal except for a slight increase in polymorphonuclear cells. Repeated urinalysis revealed a one to two plus albumin, one to two white blood cells, none to two red blood cells and an occasional hyaline cast. Sedimentation rate was 0.73 mm. per minute. Urea clearance was 111 per cent in the first hour and 59 per cent in the second hour. Routine serological test for syphilis was positive. However, verification tests and additional studies revealed this to be a false positive reaction. A roentgen-ray examination of the chest revealed an enlarged heart and pericardial effusion (figure 1). The electrocardiogram was interpreted as being consistent with the diagnosis of pericarditis.

Course in Hospital: Treatment consisted of complete bed rest, ferrous sulfate, vitamin supplements and salicylates. A few days after admission the patient developed a recurrence of her arthritis, and this as well as the fever subsided after the use of large amounts of salicylates. The pericardial effusion subsided gradually, and the venous pressure returned to normal. During this hospitalization she had a rash which was diagnosed as a contact dermatitis from the bleach used in the bed linen. She was discharged September 17, 1942, with a diagnosis of rheumatic fever and advised to continue the regimen that had been followed in the hospital and to return in three months.

She was re-admitted December 16, 1942. During her stay at home she had continued to have recurrences of the arthritis and fever, and one week prior to admission she developed a recurrence of the dyspnea. Physical examination at this time was essentially the same as that of the first admission except that no friction rub was heard. Treatment was the same as on the previous hospitalization, and the diagnosis of rheumatic fever was reaffirmed. Approximately one month after admission she developed erythema on the nose and malar eminences and subsequently a typical eruption of disseminated lupus erythematosus. Laboratory studies during this admission were as follows: Hemoglobin 75 per cent, red blood count 4,100,000 per cu. mm., white blood count 3100 to 7700 per cu. mm., urinalysis showed a three plus albumin, 5 to 10 white blood cells, 30 to 40 red blood cells, and hyaline and granular casts; urea clearance was 69 per cent in the first hour and 36 per cent in the second. Total serum proteins 9.0 gm. per 100 c.c. with the albumin being 2.1 and the globulin 6.9, making

FIG. 1. A roentgen-ray of the chest of Case 1 taken July 16, 1942. There is marked enlargement of the cardiac shadow, and the configuration is globular. There is no prominence of pulmonary vascular markings as one would expect in the presence of marked mitral stenosis with pulmonary congestion, and there is no evidence of any active pulmonary disease. The appearance of the silhouette is that of pericardial effusion.

a ratio of 0.3. The electrocardiogram and the roentgenogram of the chest were essentially the same as on the first admission. After the diagnosis of lupus erythematosus became apparent, treatment with testosterone, 25 mg. every other day, was begun, and on March 22, 1943, she had a radium implant for sterilization. In spite of the above treatment and general supportive measures, the pericardial effusion became more marked, and she developed pneumonia, pleural effusion, gallop rhythm, evidence of increasingly impaired renal function, and on April 7, 1943, she had a convulsion and died. Permission for autopsy was not granted.

Case 2. A 25 year old white married female was first admitted to University Hospital, May 16, 1946. One and a half years prior to admission she had developed numbness, pain and color changes in the tips of the fingers and toes upon exposure to cold. This recurred many times and was relieved only by heat. She was advised to go to Florida in 1945, and while there developed a dry gangrene of the tip of the right index finger which healed without difficulty. During her stay in Florida, she developed mild swelling of the ankles, wrists and proximal interphalangeal joints. She returned to her home in Michigan in 1946, and shortly afterward developed

two penny-sized erythematous lesions on either side of the nose. The eruption gradually spread to involve the malar areas, and she developed fever, malaise, generalized aching and occasional sharp, intermittent pains just to the right of the sternum. She was admitted on the neuro-surgical service to have a sympathectomy, the admitting diagnosis being Raynaud's disease and scleroderma. The diagnosis of disseminated lupus erythematosus was made by the sudden appearance of characteristic facial erythema and she was promptly transferred to the Dermatology service.

Physical Examination: Temperature 100° F., pulse 96, respirations 22, blood pressure 120/76. The patient was well developed, nourished and appeared acutely ill. There was an erythematous lesion involving the nose, chin and flush area of the face. An erythema of the volar surface of the tips of several fingers and swelling of the proximal interphalangeal joints of the middle and ring fingers of both hands were present. There was tenderness of the calf muscles and ankles. The remainder of the physical examination was essentially negative.

Summary of Laboratory Findings: All urine specimens taken during this hospitalization showed a two to three plus albumin, a few red cells, a few white cells, and a few granular casts. Her blood picture showed a mild secondary anemia and a

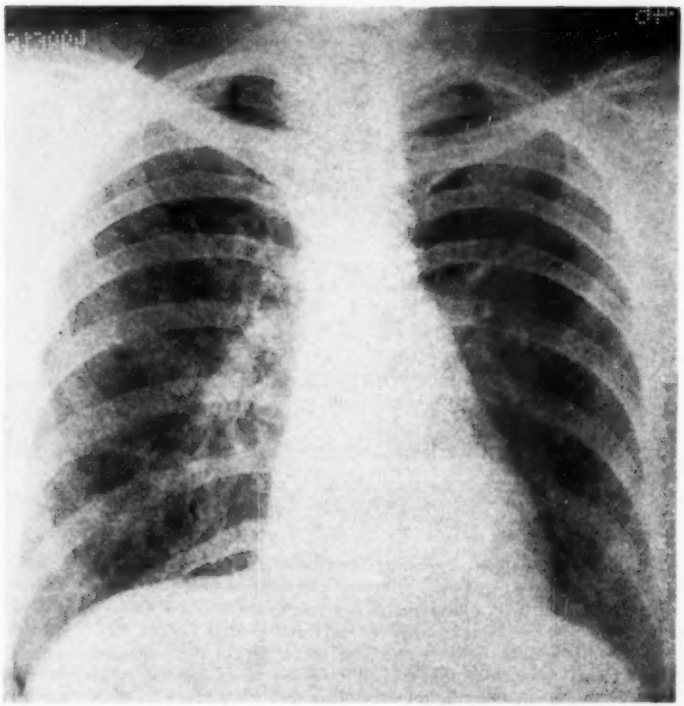


FIG. 2. A roentgen-ray of the chest of Case 2 taken May 17, 1946, during an acute exacerbation of her lupus erythematosus, but before the pericardial effusion occurred. The lung fields are clear, and the cardiac shadow is of normal size and configuration.

normal white blood cell count and differential count. Urea clearance showed 147 per cent excretion in the first hour and 70 per cent in the second. The nonprotein nitrogen was 36.2 mg. per cent. Roentgen-ray examination of the chest on admission was essentially negative (figure 2), but subsequent examinations revealed the development of cardiac enlargement, pericardial effusion (figure 3), pulmonary congestion and pleural effusions (figure 4). Examinations of the gastrointestinal tract by means of a barium meal demonstrated no abnormality. Biopsy of the gastrocnemius muscle was essentially normal.

FIG. 3. A roentgen-ray of the chest of Case 2 taken August 8, 1946. There is marked globular enlargement of the cardiac shadow, and its appearance is entirely compatible with a diagnosis of pericardial effusion.

Course in the Hospital: Treatment consisted of multiple small blood transfusions and Lugol's solution by mouth. Shortly after admission the patient showed temporary improvement with a lowering of her temperature, pulse and respirations. Subsequently, however, she developed pneumonia and cardiac failure, the former responding to penicillin and an oxygen tent and the latter to digitalization and a diuretic regimen. From time to time she had erosions on the hard palate, buttocks and shoulders. At the time of discharge on June 28, 1946, she was somewhat improved, but continued to show an enlarged heart and pericardial fluid.

The patient was readmitted to the Hospital on July 28, 1946. One week after her return home she began to develop ankle edema, epigastric discomfort, dysphagia,

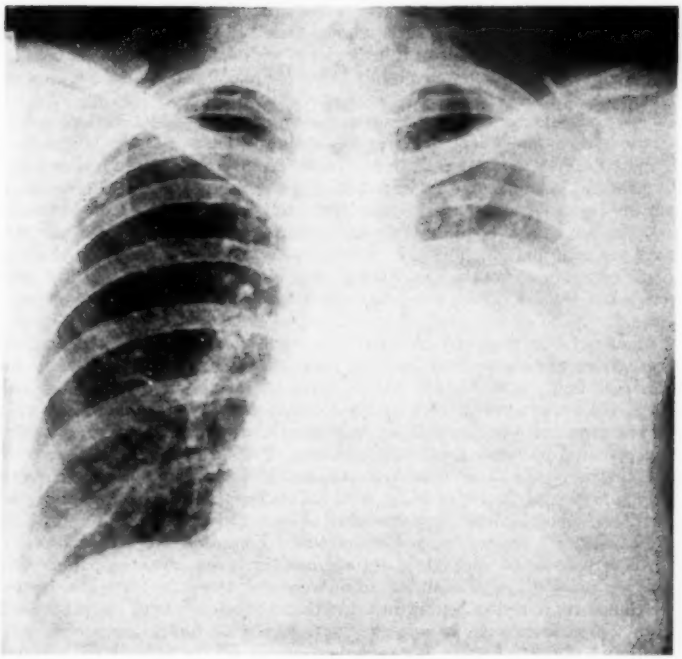


FIG. 4. A roentgen-ray of the chest of Case 2 taken August 16, 1946. There is a massive pericardial effusion as well as a left pleural effusion. Tamponade, but not myocardial failure, was present. There are suggestive signs of increased density of the parenchyma of the left lung, but the field is almost completely obscured by fluid. The right lung remains clear.

vomiting, and daily temperature elevations of 100° to 101° F. Physical examination at the time of admission revealed a chronically ill white female who was moderately dyspneic and was most comfortable when sitting up. Her temperature was 101° F., pulse 100, respirations 28 and blood pressure 106/70. There were sclerodermatous changes of the skin of the hands, wrists and arms. The face was quite clear. A small erosion was present on the hard palate. The right lung was entirely clear; there were signs of fluid at the left base. The area of cardiac dullness was enlarged to the mid-axillary line on the left and 3 cm. to the right of the sternum on the right. The sounds were faint, the rhythm regular and there were no murmurs. There was moderate distention of the abdomen with gas, and the liver edge was palpable. A moderate edema was present over the ankles and the sacrum, and minimal swelling and pain on motion of the proximal interphalangeal joints of the middle and ring fingers of both hands. The wrists were only slightly painful on motion, and there was limitation of motion of the left temporomandibular joint.

Summary of Laboratory Findings: Urinalysis on admission showed a one plus albumin, an occasional red cell, an occasional white cell, and one to two casts per high power field. The specific gravity was 1.012. Throughout the hospital stay, the urine continued to show a two or three plus albumin. The red cells and casts disappeared,

but the white cells increased until there were 10 to 15 per high power field. The specific gravity of the urine was never higher than 1.013. A routine blood examination on admission showed 86 per cent hemoglobin with 4,000,000 red blood cells per cu. mm. The white blood count was slightly elevated, 13,650 per cu. mm., with a normal differential.

An electrocardiogram taken on admission showed a P–R interval of 0.28, QRS 0.07. There were small deflections in all leads, inverted T-wave in Leads I and II and chest Leads V and VI inclusive. Total serum protein shortly after admission was 8.1 per cent, albumin 3.6 per cent and globulin 4.5 per cent. Blood nonprotein nitrogen on September 17 was 35.4 mg. per cent. Blood chloride on September 19 was 533 mg. per cent. Total serum protein on September 19 was 5.6 per cent, albumin 1.9 per cent and globulin 3.7. Roentgen-ray examinations of the chest during this admission again showed cardiac enlargement and pericardial and pleural effusions, and were taken serially during this hospitalization in order to follow the status of the effusion.

Summary of Course in the Hospital: On admission the patient was started on a diuretic regimen and showed considerable weight loss but no decrease in the amount of pericardial fluid. On August 10, the first pericardial tap was done with the removal of 420 c.c. of clear pale yellow fluid which was a typical transudate. Following this she required a pericardial tap at intervals of approximately one week, some being necessitated by acute cardiac tamponade. From 510 c.c. to 910 c.c. were removed each time. On three occasions it became necessary to do a pleural thoracentesis, approximately one liter being removed each time. Her course was gradually downward, and she required large amounts of narcotics for relief of chest pain and headaches. General supportive and symptomatic treatment were of no avail. Because of severe nostalgia and adequate facilities for home care, the patient was discharged September 22, 1946. Information received from the patient's family was that her course continued to be downward with the development of convulsive seizures and death approximately one month after discharge. No autopsy was obtained.

Discussion

The cutaneous and visceral manifestations as well as the pathological process in disseminated lupus erythematosus have been fully discussed in numerous other reports and no attempt is made to cover the disease in detail. However, the occurrence of pericardial effusion, together with ascites and pleural effusion, in this syndrome has not been clearly delineated in the past, and a review of the literature would lead one to belive that it is unusual as a clinical manifestation. The experience in this Clinic corroborates that impression, but we have seen two cases in which it presented a major problem, one case requiring five pericardial taps, and its presence in another leading to the erroneous diagnosis of rheumatic fever until the development of cutaneous lesions made the diagnosis apparent. Certainly lupus erythematosus is a disease to be considered in the differential diagnosis of pericardial effusion, especially when this finding is associated with other more common manifestations of the disorder.

Summary

Two cases of disseminated lupus erythematosus are reported. Pericarditis and the presence of small amounts of pericardial fluid at autopsy have been relatively common, but massive effusions presenting a major therapeutic problem such as occurred in one of our patients (case 2) have not been previously re-

ported. In our other patient a pericardial effusion was responsible for many of her symptoms and signs.

BIBLIOGRAPHY

1. Klemperer, P., Pollack, A. D., and Baehr, G.: Pathology of disseminated lupus erythematosus, Arch. Path., 1941, xxxii, 569.
2. Hebra, F.: Ztschr. d. k. k. Gesellsch. d. Aerzte zu Wein., 1845, i, 40, quoted by Klemperer et al.
3. Cazenave, A.: Ann. d. mal. de la peau, 1851, iii, 297, quoted by Klemperer et al.
4. Kaposi, M.: Arch. f. Dermat. u Syph., 1872, iv, 36, quoted by Klemperer et al.
5. Osler, W.: On the visceral manifestations of erythema exudativum multiforme, Am. Jr. Med. Sci., 1895, cx, 629.
6. Osler, W.: The visceral lesions of the erythema group, British Jr. Dermat., 1900, xii, 227.
7. Osler, W.: On the visceral manifestations of the erythema group of skin disease, Am. Jr. Med. Sci., 1904, cxxvii, 1.
8. Libman, E. and Sachs, B.: A hitherto undescribed form of valvular and mural endocarditis, Arch. Int. Med., 1924, xxxiii, 701.
9. Christian, H. A.: Long continued fever with inflammatory changes in serous and synovial membranes with essential glomerulonephritis: a clinical syndrome of unknown etiology, Med. Clin. N. Am., 1935, xviii, 1023.
10. Baehr, G., Klemperer, P., and Schifrin, H.: A diffuse disease of the peripheral circulation, Trans. Assoc. Am. Phys., 1935, l, 139.
11. Reifenstein, E., Reifenstein, E., Jr., and Reifenstein, G.: A variable symptom complex of undetermined etiology with fatal termination, Arch. Int. Med., 1939, liii, 553.
12. Montgomery, H.: Pathology of lupus erythematosus, Proc. Staff Meet. Mayo Clin., 1940, xv, 670.
13. Jarcho, S.: Lupus erythematosus associated with visceral vascular lesions, Bull. Johns Hopkins Hosp., 1936, lix, 262.
14. Fox, R. A.: Disseminated lupus erythematosus: an allergic disease, Arch. Path., 1943, xxxvi, 311.
15. Contratto, A. W., and Levine, S. A.: Acute lupus erythematosus, New Eng. Jr. Med., 1939, ccxxi, 602.
16. Blount, S. G., and Barrett, J. T.: Acute lupus erythematosus: a report of a case in a male with associated atypical verrucous endocarditis (Libman-Sachs), Ann. Int. Med., 1945, xxiii, 251.
17. Rose, E., and Goldberg, L. C.: The visceral lesions of acute disseminated lupus erythematosus, Med. Clin. N. Am., 1935, xix, 333.
18. Rakov, H. L. and Taylor, J. S.: Acute disseminated lupus erythematosus, Arch. Int. Med., 1942, lxx, 88.
19. Cabot Case: New Eng. Jr. Med., 1941, ccxv, 549.
20. Daly, D.: Central nervous system in disseminated lupus erythematosus, Jr. Nerv. and Ment. Dis., 1945, cii, 461.
21. Gahan, E.: Lupus erythematosus: clinical observations in 443 cases, Arch. Dermat. and Syph., 1942, xlv, 685.
22. Gitlow, S., and Goldmark, C.: Generalized capillary and arteriolar thrombosis: report of two cases with discussion of the literature, Ann. Int. Med., 1939, xiii, 1046.
23. Pillow, R. P., and Palmer, L. J.: Lupus erythematosus disseminatus, Northwest Med., 1945, xliv, 145.
24. Christian, H. A., and Rubin, M. M.: Massive edema in an acute systemic disease resembling the disseminated lupus erythema syndrome, Jr. Med. Soc. New Jersey, 1944, xli, 398.

EDITORIAL

RECENT STUDIES IN PROBLEMS OF BLOOD COAGULATION

INTEREST in the problems of blood coagulation stems not only from recent studies of those disturbances which lead to hemorrhagic manifestations, but also from those variations in the mechanism which may be responsible for hypercoagulability. The clinical use, in thromboembolic diseases, of agents, such as heparin and dicumarol, which modify the coagulability of blood has steadily increased. A rational approach to the management of spontaneous or induced disorders of the hemostatic mechanism demands consideration of concepts revised by the accumulation of new and important experimental data. The clinician attempting such a survey will be hampered to some extent by a terminology completely intelligible, perhaps, only to the select group known as "coagulationists." In some instances variations in nomenclature were undoubtedly accentuated by a war-imposed scientific hiatus between this country and some parts of Europe. This is particularly true in regard to important studies emanating from the Scandinavian countries. An effort will be made to touch briefly upon selected phases of this large problem.

Proper orientation requires a fixed point of departure. In spite of numerous other proposals there seems to be general agreement that the classical Morawitz theory of blood coagulation offers the best framework upon which new concepts can be superimposed. It will be recalled that according to this theory, coagulation takes place in two stages as illustrated by the well known formula—

$$\text{Prothrombin} + \text{Ca}^{++} + \text{Thromboplastin} \rightarrow \text{thrombin}$$
$$\text{Thrombin} + \text{Fibrinogen} \rightarrow \text{fibrin}$$

Jacques [1] observes that hemostasis represents a summation of at least three factors—formation of the fibrin clot, platelet adhesion, and the vascular response—which do not necessarily operate together in all instances of abnormal bleeding. A breakdown of one factor can exist without complete disruption of the hemostatic mechanism. This is exemplified by the recent observation of a number of instances of complete, apparently congenital, afibrinogenemia [2] in which the total inability to form a clot was associated with hemorrhagic manifestations no more severe than with mild hemophilia. Simultaneous disturbance of several aspects of the hemostatic mechanism will on the other hand usually produce a serious bleeding tendency.

Initiation of the clotting reaction requires the activity of a thromboplastic mechanism for transformation of prothrombin to thrombin. Studies of the

[1] JACQUES, L. B.: Blood clotting and hemostasis, *in* Blood Clotting and Allied Problems, The Josiah Macy Jr. Foundation, New York, N. Y., p. 9.
[2] MACFARLANE, R. G.: A boy with no fibrinogen, Lancet, 1938, i, 309.

coagulation defect in hemophilia disclosed that a plasma constituent was essential in this phase of the reaction.[3] This substance, globulin in nature, is apparently absent from the blood of hemophiliacs. Plasma fractionation technics developed by Cohn et al. have localized this anti-hemophilic globulin to so-called Fraction I.[4] Prior to the discovery of this factor all thromboplastic activity was considered to reside within the platelets. Focussing of attention upon "plasma thromboplastin" led to the assignment of the platelets to a relatively minor rôle in thrombin formation. It is now recognized, although the exact relationship is not clear, that both elements are essential for thromboplastic action. In 1946, Jacques et al.[5] introduced the technic of coating syringes, needles and glassware with silicone. Blood collected in this manner will remain fluid for several hours, apparently due to preservation of the platelets. By prolonged centrifugation in the cold in silicone coated tubes Brinkhous[6] has been able to completely remove platelets and produce an incoagulable plasma. The addition of such plasma to similarly treated hemophilic plasma did not correct the coagulation defect. On the other hand, the addition of such plasma to whole hemophilic blood containing platelets did correct the coagulation delay. Both platelets and plasma factor are essential for normal thromboplastic activity. Quick[7] has attempted to incorporate the plasma factor in the classical coagulation reaction by assigning to it the term, thromboplastinogen, to indicate its existence in an inactive state in the plasma. Vascular injury, resulting in the breakdown of platelets, liberates from them an enzyme which transforms thromboplastinogen to thromboplastin and thus permits the coagulation mechanism to proceed.

It seems clearly established that plasma contains a proteolytic enzyme, in an inactive state, which because of its characteristic behavior has been termed fibrinolysin (plasmin).[8] The inactive state is referred to as profibrinolysin (plasminogen). It is this enzyme which is transformed from an inactive to an active phase by an enzyme liberated by streptococci, known as streptokinase. The exact position of fibrinolysin in the coagulation reaction is not too clearly understood at this time. Ferguson[9] has attempted to assign to a plasma proteolytic enzyme, presumably identical with fibrinolysin, a major rôle in the initiation of clotting. According to this investigator

[3] Patch, A. J., Jr., and Stetson, R. P.: Hemophilia. II. Some properties of a substance obtained from normal human plasma effective in accelerating the coagulation of hemophilic blood, Jr. Clin. Invest., 1937, xvi, 113.

[4] Minot, G. R., Davidson, C. S., Lewis, J. H., Fagnon, H. J., and Taylor, F. H. L.: The effect in hemophilia of the parenteral administration of a fraction of the plasma globulins rich in fibrinogen, Jr. Clin. Invest., 1945, xxiv, 704.

[5] Jacques, L. B., Fidlar, E., Feldsted, E. T., and MacDonald, A. G.: Silicones and blood coagulation, Canad. Med. Assoc. Jr., 1946, lv, 26.

[6] Brinkhous, K. M.: Initiation and acceleration factors in thrombosis, *in* Blood Clotting and Allied Problems, The Josiah Macy Jr. Foundation, New York, p. 39.

[7] Quick, A. J.: Studies on the enigma of the hemostatic dysfunction of hemophilia, Am. Jr. Med. Sci., 1947, ccxiv, 272.

[8] MacFarlane, R. G., and Biggs, R.: Fibrinolysis, its mechanism and significance, Blood, 1948, iii, 1167.

[9] Ferguson, J. H.: Mechanism of blood coagulation, Am. Jr. Med., 1947, iii, 67.

plasma tryptogen (profibrinolysin?) is activated to tryptase (fibrinolysin?) by the colloidal disturbance produced by vascular damage. The proteolytic enzyme then behaves as a thromboplastic agent. This view has not been substantiated as yet.

A major advance in the study of problems of blood coagulation occurred with the introduction in 1935 of the Quick [10] method of determining prothrombin clotting time. In this procedure the addition of an excess of tissue thromboplastin and an optimal amount of calcium to oxalated plasma resulted in the rapid formation of thrombin with resultant fibrin formation and clotting. The speed of the reaction was said to depend entirely upon the concentration of prothrombin present which thus constituted the chief variable. It is not our purpose, at this time, to enter into the merits of this procedure. However, it is germane to the discussion to call attention to the recently demonstrated fact that the formation of thrombin depends not only upon the concentration of prothrombin but also upon an additional substance present in the globulin fraction of plasma which has been independently reported by several investigators. Owren refers to this material as Factor V [11] while Seegers [12] terms it AC (accelerator) globulin. A deficiency of this substance will produce delay in the formation of thrombin and thereby create a false impression concerning the concentration of plasma prothrombin. The clinical significance of this factor remains to be determined by further study. Owren has recently reported a case characterized by a hemorrhagic tendency which was associated with both a prolonged prothrombin time as well as a prolonged clotting time. In this case a deficiency of Factor V was present. The entity has already been referred to as "Owren's disease" or "parahemophilia." It is possible that previously reported instances of so-called idiopathic hypoprothrombinemia were, in reality, this entity. Recent studies by Seegers et al.[13] indicate that AC-globulin is formed in the liver and like other blood clotting factors is reduced in liver disease. Ferguson and Lewis [14] point out that AC-globulin is not identical with antihemophilic globulin. Ware and Seegers [15] suggest that AC-globulin exists in an inactive state as plasma accelerator globulin which is transformed by the initial amounts of thrombin formed in the first stage of the clotting reaction to serum accelerator globulin. The latter in turn

[10] Quick, A. J., Stanley-Brown, M., and Bancroft, F. W.: A study of the coagulation defect in hemophilia and in jaundice, Am. Jr. Med. Sci., 1935, cxc, 501.

[11] Owren, P. A.: The coagulation of blood, J. Chr. Gunderson, Oslo, 1947.

[12] Ware, A. G., Guest, M. M., and Seegers, W. H.: Plasma accelerator factor and purified prothrombin activation, Science, 1947, cvi, 41.

[13] Sykes, E. M., Jr., Seegers, W. H., and Ware, A. G.: Effect of acute liver damage on AC-globulin activity of plasma, Proc. Soc. Exper. Biol. and Med., 1948, lxvii, 506.

[14] Ferguson, J. H., and Lewis, J. H.: Accelerator globulin and antihemophilic globulin in thrombin formation from aged prothrombin and in hemophilic blood, Proc. Soc. Exper. Biol. and Med., 1948, lxvii, 228.

[15] Ware, A. G., and Seegers, W. H.: Serum AC-globulin: formation from plasma AC-globulin: role in blood coagulation; partial purification; properties; and quantitative determination, Am. Jr. Physiol., 1948, clii, 567.

speeds up the first stage of the coagulation reaction. This concept may be represented schematically, as follows—

$$\text{Prothrombin} + \text{Thromboplastin} \xrightarrow{Ca^{++}} \text{Thrombin}$$

$$\text{Plasma AC-globulin} \xrightarrow{\text{thrombin}} \text{Serum AC-globulin}$$

$$\text{Prothrombin} + \text{Thromboplastin} \xrightarrow[\text{Serum AC-globulin}]{Ca^{++}} \text{Thrombin}$$

$$\text{Thrombin} + \text{Fibrinogen} \longrightarrow \text{Fibrin}$$

Concepts regarding the hemorrhagic diatheses must not only incorporate the material just presented, but also several additional disturbances recently described. Coagulation may be retarded by the presence of circulating anti-coagulants in the blood. Two varieties have been studied. Hemophiliacs treated by the repeated infusion of whole blood, plasma or anti-hemophilic globulin may develop, on an immune basis, an antibody against the plasma factor which they lack.[16] This antibody functions as an anticoagulant rendering the patient refractory to further transfusions and thus compounding his difficulties. The plasma of such patients when added to normal blood will interfere with coagulation. Allen and Jacobson [17] have recently described a bleeding tendency apparently associated with the presence of a heparin-like substance in the circulating blood. It has been shown that dogs exposed to whole-body irradiation develop a bleeding tendency not due solely to the associated thrombocytopenia, but to a circulating anti-coagulant resembling heparin. Treatment of these animals with anti-heparin agents such as protamine and toluidine blue resulted in return of the clotting time to normal in vivo and vitro. These workers,[18] in a preliminary report, noted transient improvement in the bleeding tendencies of four patients with acute leukemia and two with idiopathic thrombocytopenic purpura after the administration of toluidine blue. In an additional report from the same clinic [19] five patients who developed a hemorrhagic diathesis following treatment with nitrogen mustard were benefited by the use of anti-heparin materials. In all studies thrombocytopenia has been present, but evidence for an additional factor has been demonstrated. This line of investigation, although of considerable interest, must still be confirmed by additional studies before generalizations can be made.

[16] Craddock, C. G., Jr., and Lawrence, J. S.: Hemophilia: a report of the mechanism of the development and action of an anti-coagulant in two cases, Blood, 1947, ii, 55.

[17] Allen, J. G., and Jacobson, L. O.: Hyperheparenemia: cause of the hemorrhagic syndrome associated with total body exposure to ionizing radiation, Science, 1947, cv, 388.

[18] Allen, J. G., Bogardus, G., Jacobson, L. O., and Spurr, C. L.: Some observations on the bleeding tendency in thrombocytopenic purpura, Ann. Int. Med., 1947, xxvii, 382.

[19] Smith, T. R., Jacobson, L. O., Spurr, C. L., Allen, J. G., and Block, M. H.: A coagulation defect produced by nitrogen mustard, Science, 1948, cvii, 474.

The rational management of hemorrhagic disorders and the clinical use of anticoagulant therapy not only require detailed information of the various phases of the coagulation reactions, but also knowledge of some of the inadequacies of clinical testing of these reactions. This brief review of some of the more significant studies in this active field may serve to indicate that our former concepts of the blood coagulation process are constantly being expanded and modified and that recent gains in knowledge of new factors in this mechanism may have clinical applications.

M. S. S.

REVIEWS

Treatment of Rheumatism. 4th edition. By W. S. C. COPEMAN, O.B.E., M.A., M.D., F.R.C.P. 258 pages; 14.5 × 22 cm. The Williams and Wilkins Company, Baltimore, Md. 1946. Price, $4.00.

This book is written expressly for general practitioners. The author, a general physician, has endeavored to survey the whole field of rheumatism impartially, and to concentrate on practical therapeutic methods.

The first 108 pages consist of a series of chapters on rheumatic diseases: Acute rheumatic fever; chorea; non-articular rheumatism and fibrositis; sciatica; neuritis; gout; rheumatoid and osteo-arthritis, and spondylitis. Each chapter consists of a short clinical description and discussion of the disease in question, followed by a general outline of appropriate treatment. In the remaining 150 pages the author takes up a more detailed discussion of each form of treatment separately, describing technics and discussing their indications. Among the forms of therapy dealt with in this manner are drugs, diet, the eradication of focal sepsis, vaccines, physical methods including heat, massage, movement and exercise, manipulation, baths, colonic therapy, hormones, actinotherapy and orthopedics.

In a common sense way the author presents to the practitioner a summary of practical methods and indicates his own personal experience of each. He shows how easily many physical methods can be applied in the home, without expensive or cumbersome apparatus, but none the less effectively. He adopts the sane attitude towards osteopathy that we should not condemn what we do not understand; the osteopath makes calamitous mistakes through his ignorance of pathology, while we miss opportunities to help our patients by ignoring the undoubted successes of the osteopath. The author believes that the ability to perform simple manipulative measures should be part of the equipment of every practising physician. The final chapter is a brief one on prognosis.

The book is easy to read. The print is excellent and, although in places expression leaves much to be desired, it is written in lucid, conversational style. It is hard to accept all the author's claims and some of the reasons presented to explain the success of certain measures. But the book undoubtedly achieves its purpose, and leaves the reader with the salutary feeling that, even in its most chronic form, rheumatism is a far from dull and hopeless field. Much can be done to relieve, if not to cure, its victims.

H. L. M.

Management of Common Gastro-Intestinal Diseases. Edited by THOMAS A. JOHNSON. 280 pages; 16 × 24 cm. J. B. Lippincott Company, Philadelphia. 1948. Price, $7.00.

This product of 22 authors is a small book in relatively large type. The 16 chapters present the more important, commoner gastrointestinal conditions.

A few are excellent, particularly those on the recognition of gastric malignancy, management of bleeding peptic ulcer, amebiasis, and enterogastrone. The chapters on pancreatic disease are stimulating but not particularly applicable to clinical practice.

Many chapters are fairly elementary in discussion and definition. A few authors seem to be battling for recognition. Some write in a controversial tone. However, on the whole the book furnishes a good review for clinicians with some knowledge

of the field. It is not to be unreservedly recommended to students nor as a guide to physicians without hospital facilities.

C. B. A.

Cardiovascular Diseases. By DAVID SCHERF, M.D., F.A.C.P., Assoc. Prof. Medicine, New York Medical College, and LINN J. BOYD, M.D., F.A.C.P., Prof. Medicine, New York Medical College. 478 pages; 18.5 × 26 cm. J. B. Lippincott Co., Philadelphia. 1947. Price, $10.00.

A great deal of excellent material is concisely presented in this book and practically all aspects of cardiovascular diseases are covered. The sections on myocarditis and autonomic reflexes are especially worthwhile.

As one could readily judge from the number of pages, this is not an exhaustive text. The authors present their own views and cover the subjects with reasonable completeness, omitting detailed discussion on controversial points. The resulting brevity will be welcomed by medical students and physicians interested in reviewing cardiovascular diseases. Both groups will find the material easy to read and understand. For those specializing in cardiovascular diseases the book obviously would not serve as a comprehensive reference work.

To this reviewer the only major defect seems to be in the arrangement of subjects. Chapters follow each other without definite order, related subjects often being widely separated in the table of contents. This causes some lack of continuity in the text, which is not wholly compensated by the index and the rather full table of contents. For instance, there are 14 index references to the subject of shock, and yet, in none of these instances is this important subject covered very fully. It would seem that the book's value would be greatly enhanced by better organization.

E. E. L.

Breast Feeding: A Guide to the Natural Feeding of Infants. By F. CHARLOTTE NAISH. 151 pages; 13 × 19 cm. Oxford University Press, New York. 1948. Price, $3.50.

This small book is basically an appeal for an increase in the frequency of the breast feeding of infants. The advantages of this natural method of feeding are stressed throughout. Frequent comparisons between the udder of the cow and the breasts of the mother are made and form the basis for pre- and post-natal breast care. The author advocates several questionable forms of therapy, such as the use of thyroid extract in the torporous infant to encourage the infant to take the offered feedings. The initial chapter, "The Mind of the Mother," is very well written and is highly recommended to all who deal with infant feeding.

J. E. B.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Conditioned Reflexes and Neuron Organization. By JERZY KONORSKI, Head of the Department of Neurophysiology in the Nencki Institute of Experimental Biology, etc. Translated from the Polish MS. under the author's supervision by STEPHEN GARRY. 267 pages; 22.5 × 14.5 cm. 1948. Cambridge, at the University Press; New York, The Macmillan Company. Price, $4.00.

Diabetic Manual for the Doctor and Patient. 8th Ed. By ELLIOTT P. JOSLIN, M.D., Sc.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc. 260 pages; 20.5 × 14 cm. 1948. Lea & Febiger, Philadelphia. Price, $2.50.

Diseases of the Adrenals. 2nd Ed. By LOUIS J. SOFFER, M.D., Associate Attending Physician, The Mount Sinai Hospital, New York City, etc. 320 pages; 24 × 15.5 cm. 1948. Lea & Febiger, Philadelphia. Price, $6.50.

Education for Professional Responsibility. A Report of the Proceedings of the Inter-Professions Conference on Education for Professional Responsibility held at Buck Hill Falls, Pennsylvania, April 12, 13, and 14, 1948. 207 pages; 21.5 × 14 cm. 1948. Carnegie Press, Carnegie Institute of Technology, Pittsburgh. Price, $3.00 (Orders should be sent to distributor, Rutgers University Press, New Brunswick, New Jersey.)

Estudio Clínico del Enfisema Pulmonar. By JOSE ARMANDO SCIUTO. 165 pages; 24.5 × 17 cm. (paper-bound). 1947.

For Doctors Only. By FRANCIS LEO GOLDEN. With a Foreword by WILLIAM E. MOUNTFORD, M.D., and illustrated by BARYE PHILLIPS. 273 pages; 21 × 14 cm. 1948. Frederick Fell, Inc., New York. Price, $2.95.

Hematology. By CYRUS C. STURGIS, M.D., Professor of Internal Medicine, Chairman of the Department of Internal Medicine, University of Michigan Medical School, etc. 915 pages; 26 × 17 cm. 1948. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $12.50.

Hope in Heart Disease: The Story of Louis Faugères Bishop, M.D. By RUTH V. BENNETT. 307 pages; 21 × 14.5 cm. 1948. Dorrance & Company, Philadelphia. Price, $3.00.

An Introduction to Gastro-enterology. 4th Ed. By WALTER C. ALVAREZ, Professor of Medicine, University of Minnesota, etc. 903 pages; 26 × 18.5 cm. 1948. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $12.50.

List of Species Maintained in the National Collection of Type Cultures. Medical Research Council Memorandum No. 21. 17 pages; 24.5 × 15.5 (paper-bound). 1948. His Majesty's Stationery Office, London. Price, Ninepence net.

Mineral Nutrition of Plants and Animals. By FRANK A. GILBERT. 131 pages; 23.5 × 16 cm. 1948. University of Oklahoma Press, Norman. Price, $2.75.

Pathology. Edited by W. A. D. ANDERSON, M.A., M.D., F.A.C.P., Professor of Pathology and Bacteriology, Marquette University School of Medicine, Milwaukee. 1453 pages; 25.5 × 17.5 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, $15.00.

Physicians' Federal Income Tax Guide for the Preparation of 1948 Returns and 1949 Estimates—1948–49 Edition. By HUGH J. CAMPBELL and JAMES B. LIBERMAN. 95 pages; 28 × 21.5 cm. (paper-bound). 1948. Doniger & Raughley, Inc., Great Neck, New York. Price, $2.50.

Post-mortem Appearances. 5th Ed. By JOAN M. ROSS, M.D., B.S. (Lond.), M.R.C.S., L.R.C.P., Advisor in Pathology to the Ministry of Supply, etc. 308 pages; 17 × 11 cm. 1948. Oxford University Press, New York. Price, $2.75.

The Skin Diseases: A Manual for Practitioners and Students. By JAMES MARSHALL, M.D., B.S., M.R.C.S., L.R.C.P., Consulting Dermatologist, Central Middlesex County Hospital, etc. 363 pages; 22 × 14.5 cm. 1948. Cambridge, at the University Press; New York, The Macmillan Company. Price, $7.50.

Tuberculosis in Childhood. 2nd Ed. By DOROTHY STOPFORD PRICE, M.D. (Univ. Dublin), Physician, St. Ultan's Infant Hospital, Dublin, etc. With a Chapter on Tuberculous Orthopaedic Lesions and Other Contributions by HENRY F. MACAULEY, M.Ch., F.R.C.S.I., Orthopaedic Surgeon, Mater Misericordiae Hospital, Dublin, etc. 219 pages; 19 × 13 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $7.00.

COLLEGE NEWS NOTES

Nominations for A.C.P. Elective Offices, 1949–50

In accordance with the By-Laws of the American College of Physicians, **Article I,** Section 3, the following nominations for the elective offices, 1949–50, are herewith announced and published:

President-Elect ..... William S. Middleton, Madison, Wis.
First Vice President ..... George F. Strong, Vancouver, B. C.
Second Vice President ..... Roy R. Snowden, Pittsburgh, Pa.
Third Vice President ..... Turner Z. Cason, Jacksonville, Fla.

Regular elections will take place at the 1949 Annual Session in New York City, March 28–April 1. The Annual Business Meeting will be held Thursday afternoon, March 31, in the Grand Ballroom of the Waldorf-Astoria Hotel.

The election of nominees shall be by the Fellows and Masters of the College. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations for members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,
A. B. Brower, Dayton, Ohio
Harold H. Jones, Winfield, Kans.
Chester S. Keefer, Boston, Mass.
T. Homer Coffen, Portland, Ore.
Maurice C. Pincoffs, Chairman, Baltimore, Md.
Committee on Nominations

Proposal of Candidates

The By-Laws of the American College of Physicians require that candidates for election to Associateship or Fellowship shall be proposed on the official forms by Fellows from the same cities or areas as the candidates. Furthermore, these proposals must be filed at the College headquarters at least 60 days in advance of action on them by the Credentials Committee. The Committee will next meet on February 26 and 27, 1949, and will examine credentials received up to 60 days beforehand. The Committee will again meet on March 26, 1949, and November, 1949.

Associates Should Attend A.C.P. Annual Session

Attendance at one or more Annual Sessions by Associates before proposal for advancement to Fellowship is prescribed by regulations of the Board of Regents of the American College of Physicians. This regulation was temporarily discontinued during World War II from 1942 to 1946, because it became obviously impossible for Associates in the armed services to attend and because the Annual Sessions of the College had been abandoned during part of that time. The regulation is now again in full effect. It is maintained that an Associate must display an abiding interest in the College and in internal medicine or its allied branches. There is no better way in which such an interest can be displayed than by attendance at the Annual Sessions of the College, accepted as the most important postgraduate week in the field on this Continent.

The tentative program of the 30th Annual Session, which will be held at the Waldorf-Astoria Hotel, New York, N. Y., March 28–April 1, 1949, will be published in the February issue, the Convention Number.

Colorado Regional Meeting Announced

The Regional Meeting of the American College of Physicians, for its members in Colorado and their guests, will be held in Denver on March 1, 1949. Preparations for the meeting are being made by Ward Darley, M.D., F.A.C.P., Governor for Colorado, and Louis S. Faust, M.D., F.A.C.P., Chairman of Arrangements. The program will be printed and distributed to members in the State.

Kentucky Regional Meeting

Members of the College, in Kentucky, and their guests enjoyed a very interesting meeting on the afternoon and evening of December 4, 1948. Held at St. Joseph's Hospital and the Phoenix Hotel in Lexington, the scientific session included speakers from a number of Kentucky cities and an address by Walter L. Palmer, M.D., F.A.C.P., Chairman of the Board of Governors of the College. Thornton Scott, M.D., F.A.C.P., Lexington, served as Presiding Officer at the afternoon session and J. Murray Kinsman, M.D., F.A.C.P., Louisville, Governor for Kentucky, was Toastmaster at the dinner.

The scientific program was as follows:

Unusual Manifestations of Myxedema: a Case Report.
Thornton Scott, M.D., F.A.C.P., Lexington.

Methods of Liver Biopsy, with Reference to a New Type of Needle.
Franklin B. Moosnick, M.D. (Associate), Lexington.

The Addiction Liability of Keto-bemidone, a New Derivative of Demerol.
Harris Isbell, M.D. (Associate), U. S. Public Health Service Hospital, Lexington.

Gold Therapy in Rheumatoid Arthritis.
Joseph T. Gilbert, Jr., M.D., F.A.C.P., Bowling Green.

Unusual Instances of Hemorrhage from the Gastrointestinal Tract.
George N. Burger, M.D., F.A.C.P., Covington.

Eastern Pennsylvania Regional Meeting

The 11th Annual Round-up of Eastern Pennsylvanians was held in Philadelphia, December 10, 1948, under the Governorship of Edward L. Bortz, M.D., F.A.C.P., Philadelphia, who served as Presiding Officer and Toastmaster. The meeting began with a buffet luncheon at the College Headquarters and continued with a scientific program at the College of Physicians of Philadelphia, and a dinner meeting in the evening at the Warwick Hotel. The afternoon session was arranged by collaboration between Governor Bortz and Henry L. Bockus, M.D., F.A.C.P., who was currently conducting an A.C.P. postgraduate course in gastro-enterology. Approximately 400 members and their guests attended this session.

The dinner meeting was enthusiastically attended. In addition to several Governors of adjacent areas, the deans of Philadelphia medical schools were present. A.C.P. President Walter W. Palmer, and Executive Secretary E. R. Loveland addressed the gathering; and an outstanding talk on "Medicine and the National Security Resources Board" was delivered by James A. Crabtree, M.D., Director of the Medical

Service Division of the Board. For the members of Eastern Pennsylvania, Edward W. Bixby, Sr., M.D., F.A.C.P., Wilkes-Barre, presented Dr. Bortz an engraved gavel as a token of appreciation of his fine representation of the group during the past several years.

The following papers were presented during the scientific meeting:

The Prognosis in Coronary Artery Disease.
WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., Professor of Medicine, Woman's Medical College of Pennsylvania, Philadelphia.

Diffuse Hepatic Necrosis.
CLARK E. BROWN, M.D. (by invitation), Pathologist, Lankenau Hospital, Philadelphia.

Fat Metabolism and Vascular Degeneration.
SIDNEY WEINHOUSE, Ph.D. (by invitation), Director of Biochemical Research, Temple University Research Institute, Philadelphia.

Significant Developments in Army Medical Research.
GEORGE E. ARMSTRONG, Brigadier General (MC), USA, Deputy Surgeon General, Washington, D. C.

Differential Diagnosis of Jaundice.
HENRY J. TUMEN, M.D., F.A.C.P., Associate Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine, Philadelphia.

The So-called Post-Cholecystectomy Syndrome.
HENRY L. BOCKUS, M.D., F.A.C.P., Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine, Philadelphia.

The Physiologist's Concept of Biliary Dyssynergia.
S. S. KETY, M.D. (by invitation), Professor of Clinical Physiology, University of Pennsylvania Graduate School of Medicine, Philadelphia.

The 77th Annual Meeting of the American Public Health Association will be held in New York City the week of October 23, 1949.

THE AMERICAN BOARD OF PEDIATRICS, INC.; John McK. Mitchell, M.D., Executive Secretary; 6 Cushman Road, Rosemont, Pa. Oral examinations will be held at St. Louis, Mo., on February 17, 18 and 19, 1949, and at Baltimore, Md., on May 7, 8 and 9, 1949.

HOTEL ACCOMMODATIONS, 30TH ANNUAL SESSION

Directions and forms for making hotel reservations during the 30th Annual Session, New York City, March 28–April 1, 1949, were mailed to all members of the College during December. It is hoped that the members will follow these directions and will enter their reservations at the earliest possible moment so as to assure themselves of the type of accommodation desired. An adequate number of rooms has been provided; however, the hotels will appreciate it if arrangements are made, whenever possible, for occupancy of rooms accommodating two persons.

Reservations will be acknowledged by direct confirmation from the hotels. If an applicant subsequently finds it impossible to attend the session, he is requested to

send notification promptly to the Housing Bureau, The American College of Physicians, c/o New York Convention Bureau, 500 Park Avenue, New York 22, N. Y.

The American College of Physicians makes grateful acknowledgment of the contribution by Cyrus C. Sturgis, M.D., F.A.C.P., to the College Library of Publications by Members, of a copy of his book, "Hematology," published by Charles C. Thomas, Springfield, Ill., 1948.

Mississippi Valley Medical Society 1949 Essay Contest

The Ninth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1949. The Society will offer a cash prize of $100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States. The winner will be invited to present his contribution before the Fourteenth Annual Meeting of the Mississippi Valley Medical Society to be held in St. Louis, Mo., Sept. 28, 29, 30, 1949, the Society reserving the exclusive right to first publish the essay in its official publication—the *Mississippi Valley Medical Journal* (incorporating the *Radiologic Review*). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1949. The winning essays in the 1948 contest appear in the January 1949 issue of the *Mississippi Valley Medical Journal* (Quincy, Illinois).

Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209–224 W. C. U. Building, Quincy, Illinois.

Additional Life Members

The American College of Physicians takes pleasure in announcing that the following Fellows have become Life Members of the College by their recent subscriptions:

Joseph Hughes, M.D., Philadelphia, Pa.
George B. Dorff, M.D., Brooklyn, N. Y.
G. A. Westfall, M.D., Halstead, Kans.
Milford O. Rouse, Dallas, Tex.

Post-Convention Cruise to Bermuda

You are in "Merrie England" as soon as you leave the Pier in New York and you will be under the flag of Great Britain until your return.

You will enjoy the new *Queen of Bermuda*, the spacious lounges, the cozy settings for chats, quiet reading, or spicy cocktails. The stewards take pride in carrying out the tradition of courtly service. The food is international, prepared by chefs trained in the best restaurants of Europe. Whether you order veal and ham pie, a Yorkshire pudding, chicken Maryland, or other traditional dish, you will enjoy it.

We shall use two hotels in Bermuda. The Princess stands at the water's edge. The Bermudiana stands on a small bluff directly above the blue waters. These hotels are the best in the islands. Both have magnificent views overlooking the lovely harbor and hills beyond and are only five to ten minutes by pleasant walks from the fascinating shops.

The Princess Hotel and guest cottages, overlooking the blue waters of Hamilton Harbor, just west of the city.

The newly-opened Bermudiana Hotel, well known to Bermuda's visitors. In lower right-hand corner, the Royal Bermuda Yacht Club.

Bermuda is intriguing, beautiful, picturesque, irresistible. It is a land of cedars and blossoms; sloping green hillsides; charming bays and beaches; of white and pastel coral cottages; and a tempo that makes you forget time and care. The Easter lilies, the bougainvillae, the hibiscus and the Bermuda morning glory will greet you.

The cruise itinerary gives you two and a half days in Bermuda. You may extend your stay if you so desire. While there, you will want to visit the Sea Gardens where coral polyp still shapes its strange life under the water in fans, rods and many fantastic shapes. You will also want to visit the spectacular caves, Leamington and Crystal. The latter is viewed for the most part from pontoon bridges. The water giving back the overhead reflections makes it a place of bewildering beauty.

Decide now and go. You will benefit by a decision *now*. The accommodation at all rates is limited and the demand for Bermuda space in the Spring is always very heavy. If you see any possibility of going, make your reservation; cancel later if you must. Yes, your money back, of course!

For answers to your questions, plan of ship, Bermuda booklet, etc., write AT ONCE to Leon V. Arnold, 36 Washington Square West, New York 11, N. Y. Mr. Arnold was our cruise director in 1938 and will accompany the party this year.

OBITUARIES

DR. EDWARD RHODES STITT

Edward Rhodes Stitt, Rear Admiral, Medical Corps, United States Navy, Retired, a Fellow of the American College of Physicians since 1923 and member of the Board of Regents from 1923 to 1926, died in the U. S. Naval Hospital, Bethesda, Md., on November 13, 1948, in his 81st year.

Dr. Stitt acquired his early education in a private school, and later entered the University of South Carolina where he gained his A.B. degree in 1885. He then transferred to the University of Pennsylvania and studied under Sir William Osler, graduating with the degree of Doctor of Medicine in 1889. He was accepted in the Medical Corps of the Navy upon graduation and commissioned Assistant Surgeon in March, 1889, his first commission being signed by President Benjamin Harrison. His first few years in the Navy were spent in assignments ashore and afloat, including duty in the *U.S.S. Baltimore*, one of the vessels of the famous "White Squadron," when that crack cruiser sailed for Valparaiso during the Balmacedist uprising in Chile.

In August, 1896, he was on duty in the Bureau of Medicine and Surgery where he served during the Spanish American War. In 1902 he was selected as instructor of tropical medicine and bacteriology at the newly established Navy Medical School in Washington, D. C. In 1905 he was ordered to London where he studied under Sir Patrick Manson at the famous London School of Tropical Medicine, graduating with distinction from that school. After completing the course, he went to Manila, Canacao, and Olongapo, Philippine Islands, and to Guam, Yokohama and Honolulu, in connection with the study of tropical diseases.

He was promoted to the rank of Rear Admiral in 1917. In 1920 he was selected by President Wilson to be Surgeon General of the Navy, and was reappointed in 1924 by President Coolidge. He was Inspector of Medical Department Activities of the West Coast during his last three years of active duty, retiring from active duty in 1931, after 42 years service. During his administration as Surgeon General he devoted much attention to hospital administration, and aviation medicine was established as an official specialty.

As a teacher of tropical medicine at the newly established Navy Medical School, he did much to make this the principal center for the study of tropical diseases in the United States, and the leading school of postgraduate instruction for medical officers in this specialty. Concurrently with his duties at the Medical School, he was professor of tropical medicine at both George Washington and Georgetown Universities, and also delivered frequent lectures on tropical medicine at the Jefferson Medical College of Philadelphia.

Admiral Stitt was the author of "Diagnostics and Treatment of Tropical Diseases," and of "Practical Bacteriology, Hematology and Parasitology," the latter now in its 10th edition, both published by The Blakiston Company; and he made many contributions to medical literature.

He was associate professor of medical zoölogy in the University of the Philippines; and, from 1941, he held appointment as consultant in tropical medicine to the Secretary of War. A former president of the National Board of Medical Examiners, he was a member of the Federal Board of Hospitalization and of executive and central committees of the American Red Cross.

The many honors and awards received by Admiral Stitt included the Navy Cross, "for exceptionally meritorious service in the duty of great responsibility in connection with the U. S. Navy Medical School, and in connection with the general sanitation and military work at the school and throughout the service"; he held honorary degrees of LL.D., University of South Carolina, 1917, and University of Michigan in 1921;

Sc.D., Jefferson Medical College of Philadelphia, 1920, and University of Pennsylvania, 1924; Ph.M., Philadelphia College of Pharmacy and Science, 1921. In 1942 he received the Gorgas medal from the Association of Military Surgeons. The citation accompanying the presentation read in part, "To a distinguished scholar and authority of international fame in tropical medicine." He was also a recipient of the Theobald Smith and Richard Pearson Strong medals.

Admiral Stitt was a past president of the Association of Military Surgeons of the United States and American Society of Tropical Medicine; a member of American Association of Immunologists, Association of American Physicians, American Public Health Association, Royal Society of Medicine, and Southern Medical Association; a fellow of the American Medical Association.

The Navy Medical Corps' premier physician, officer and gentleman, scientist, author and scholar, the personification of the thought embodied in the verse entitled "The Things That Are Most Excellent":

"The grace of friendship—mind and heart
Linked with their fellow heart and mind;
The gains of science, gifts of art;
The sense of oneness with our kind;
The thirst to know and understand,
A large and liberal discontent;
These are the goods in life's right hand,
The things that are more excellent."

PAUL F. DICKENS (MC), USN, Retired, F.A.C.P.

DR. JOSEPH FRANCIS BREDECK

Dr. Joseph Bredeck exercised a highly important influence in the field of public health in St. Louis from 1920 to 1925, when he was Controller of Tuberculosis, and later as Health Commissioner, from 1933 to the time of his death, October 4, 1948.

In this latter position he was widely recognized for his persistent efforts in the direction of improving the public laws pertaining to health. His name is honored chiefly for two important contributions: first, the establishment of a model milk ordinance, which, while it resulted in much controversy on the part of producers and dairies, was nevertheless in the public interest; second, for his clean restaurant law which had an immediate and drastic effect of converting the previously filthy places into clean agencies for the dispensing of food.

Dr. Bredeck was 58 years old at the time of his death. He received his A.B. at Christian Brothers College in 1910, and his M.D. from Washington University in 1914. He received the degree of D.P.H. from the University of Pennsylvania in 1917. He spent a year in the Henry Phipps Institute in Philadelphia, and later in Germany.

He saw service in World War I from 1917 to 1919. Formerly an Instructor in Washington University School of Medicine, he later became Director of the Department of Public Health of St. Louis University. He was a member of the St. Louis and Missouri Medical Societies, and the American Medical Association, National Tuberculosis Association, and was elected a Fellow of the American College of Physicians in 1929.

His departure from the scene at a relatively early age emphasized the loss which the community of St. Louis suffered. The American College of Physicians deeply regrets the loss of such an outstanding member.

RALPH KINSELLA, M.D., F.A.C.P.,
Governor for Missouri

DR. ROSS McCLURE CHAPMAN

On September 24, 1948, Baltimore and the State of Maryland suffered a great loss in the death of Dr. Ross McClure Chapman, of Towson, Md.

Dr. Chapman was born in Belleville, N. Y., on July 13, 1881. He attended Union Academy and Syracuse University, and took his medical degree in 1905 at the University of Michigan. Following his internship in the Utica, N. Y., State Hospital, he became Junior Physician in the Binghamton State Hospital (1908–16) and then went to St. Elizabeths Hospital, Washington, D. C., where, from 1916 to 1919 he progressed from Assistant Physician to Clinical Director. From 1920 on he served as Medical Superintendent of the Sheppard and Enoch Pratt Hospital, in Towson. It must be mentioned here that, under his supervision, the work at the Sheppard and Enoch Pratt Hospital grew in scope and value to the community. Along with this, Dr. Chapman was Professor of Psychiatry in the University of Maryland School of Medicine, and many fine students have followed in his footsteps from his teachings.

Dr. Chapman was a diplomate of the American Board of Psychiatry and Neurology, a past president of the Washington Psychoanalytic Society, the American Psychopathological Association, and the American Psychiatric Association. He was also a member of the Washington Society of Mental and Nervous Diseases, the American Psychoanalytic Association and the American Medical Association. He was a consultant in psychiatry to the U. S. Public Health Service from 1940 on. Dr. Chapman was elected to Fellowship in the American College of Physicians in 1931.

The last two years of his life were kept up to the best of his ability under the great handicap of a cardiovascular situation. His loss to our community will be hard to replace.

WETHERBEE FORT, M.D., F.A.C.P.,
Governor for Maryland

DR. RALPH BERNSTEIN

The death of Dr. Ralph Bernstein in Philadelphia, on November 19, 1948, brought a great sense of loss to his many friends and patients, but especially to his colleagues at the Hahnemann Medical College where he had been Professor of Dermatology since 1915.

Dr. Bernstein was born in Columbia, Pa., on April 12, 1877. He received his M.D. degree from the University of Pennsylvania School of Medicine in 1903, and also from Hahnemann Medical College and Hospital of Philadelphia in 1904, the staff of which institution he joined the same year.

Dr. Bernstein has been Consulting Dermatologist to the Shriners' Hospital for Crippled Children and Women's Homeopathic Hospital, in Philadelphia; Allentown State Hospital; J. Lewis Crozer Home for Incurables and Homeopathic Hospital, in Chester; Homeopathic Hospital, Pottstown; Homeopathic Hospital of Chester County, West Chester; West Jersey Homeopathic Hospital, in Camden. A Fellow of the American College of Physicians since 1920, Dr. Bernstein was a member of the American Academy of Dermatology and Syphilology, Society for Investigative Dermatology, American Association for the Advancement of Science, American Editors and Authors Association, American Academy of Political Science, and various state and local homeopathic societies. He was the author of four textbooks on skin diseases, and had contributed more than one hundred articles to medical journals.

Dr. Bernstein's memory will be cherished by many people, and his influence will long be felt by the physicians who trained under him.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. GEORGE WILLIAM ROSS

Dr. Ross, who became a Fellow of the American College of Physicians in 1927, died on June 13, 1948, after a lengthy illness which compelled his retirement from active practice in 1933.

Born in Strathroy, Ont., in 1877, the youngest son of Hon. Sir George and Lady Catherine Ross, he was educated in Upper Canada College and the University of Toronto, graduating in Medicine in 1902. He pursued postgraduate studies in England, notably under Sir James MacKenzie in cardiology and Sir Almroth Wright in immunology. On returning to Toronto, he joined the staff in therapeutics, and carried on private practice until ill health compelled his retirement.

Dr. Ross was a member of the Royal College of Physicians of London, and the Canadian, Ontario and British Medical Associations. He was a former vice-president of the American Immunological Association. His wife predeceased him some years ago and his two sons lost their lives in World War II.

Possessed of a keen, inquisitive mind, and a genial disposition, Dr. Ross will be greatly missed by his colleagues and friends, and his death is a distinct loss to the medical profession.

H. K. Detweiler, M.D., F.A.C.P.,
Governor for Ontario

DR. W. GRADY MITCHELL

Dr. W. Grady Mitchell of San Angelo, Tex., died in Seattle, Wash., on October 8, 1948. He had had one or two myocardial infarcts earlier in the year.

Dr. Mitchell was born in Franklin County, Va., July 17, 1896. He graduated from the University of Tennessee College of Medicine in 1921, and served his internship at the Philadelphia General Hospital, 1921–24. Following this, Dr. Mitchell pursued postgraduate studies at the University of Pennsylvania and in England, Germany and Austria. He then became physician to the Pennsylvania Hospital, which position he occupied from 1930 to 1935. He was an instructor in medicine in the University of Pennsylvania School of Medicine during this time. In the latter year, he removed to San Angelo and became cardiologist and director of clinical laboratories of St. John's Hospital. He was, also, a member of the staff of the Shannon West Texas Memorial Hospital of that city. He served as a Lieutenant Commander, United States Naval Reserve, 1940–44. Dr. Mitchell served as president and secretary of Tom Green Eight Counties Medical Society; he was a member of the Texas Heart and Southern Medical Associations, and a fellow of the American Medical Association. Since 1939 he had been a Fellow of the American College of Physicians.

Dr. Mitchell was highly esteemed and enjoyed a large consultation practice in cardiology. He is mourned by a host of friends, professional and lay, who miss his genial personality and individualism for which he will be long remembered.

David W. Carter, Jr., M.D., F.A.C.P.,
Governor for Texas

DR. MANFRED KRAEMER

Manfred Kraemer, M.D., a Fellow of the American College of Physicians since 1935, died in Newark, N. J., on Friday, November 12, 1948, in his forty-fourth year. His death was due to coronary occlusion.

He was a native of New Jersey and received his college and medical degrees from the University of Pennsylvania. He interned at the Newark City Hospital, following which he entered the practice of internal medicine and gastro-enterology in Newark.

He did extensive postgraduate work at the University of Vienna and the London School of Tropical Medicine. He was certified by the American Board of Internal Medicine in internal medicine and gastro-enterology. He rose in prominence quickly and was recognized as one of the outstanding gastro-enterologists in the State.

Dr. Kraemer was visiting physician and chief of the Gastrointestinal Department of the Newark Presbyterian Hospital, gastroenterologist to St. James Hospital, and associate visiting physician, Newark City Hospital. He was a consultant at the Irvington General Hospital. He was formerly an instructor in the New York Medical College and a postgraduate lecturer at New York University.

He was a member of many societies including the Academy of Medicine of Northern New Jersey; Royal Society of Tropical Medicine and Hygiene (England); International Gastro-Enterological Society; American Gastro-Enterological Association; American Society of Tropical Medicine; Association of Military Surgeons; and the American Gastroscopic Club.

Early in World War II, Dr. Kraemer enlisted and served as a Lieutenant Colonel in the Medical Corps, A.U.S. He was chief of the gastro-intestinal service, 188th General Hospital, and chief of medical service, 121st and 242nd General Hospitals.

He wrote numerous articles on gastro-enterology which appeared in various medical journals. He was very active in many of the organizations with which he was connected and appeared frequently on the programs as a speaker.

Dr. Kraemer was an earnest and conscientious worker in internal medicine; his chief interest, however, lay in diseases of the gastrointestinal tract. He was a skilled physician, highly regarded in his community. His high standards in life and in the practice of medicine deepen the loss of his passing to his family and the community.

JEROME G. KAUFMAN, M.D., F.A.C.P.

DR. ALVA BROWN CRADDOCK

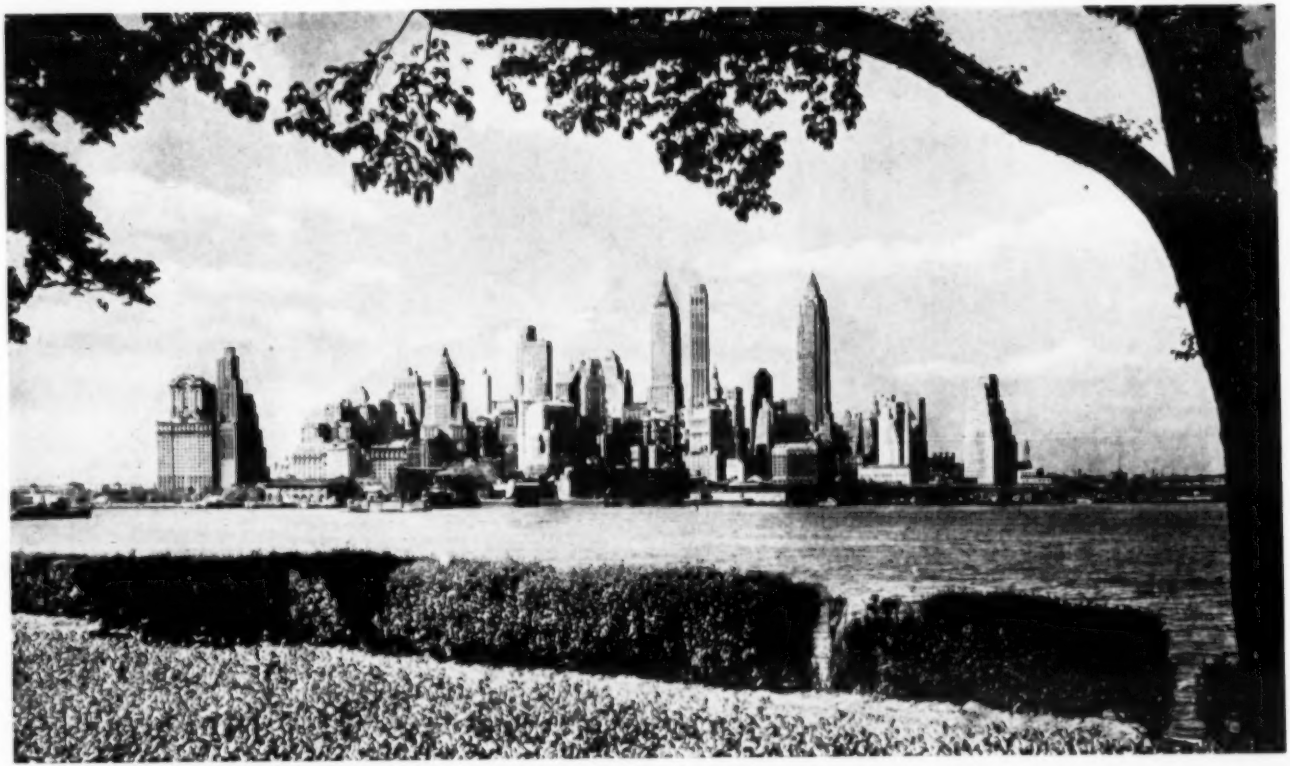
Alva Brown Craddock, M.D., F.A.C.P., died July 29, 1948, after an illness of eight months.

Dr. Craddock was born in Jackson's Gap, Ala., January 26, 1889. He attended Howard College in Birmingham where he obtained the degrees of B.S., 1908, and M.S., 1909. In 1911 he entered Johns Hopkins University and, after three years of study, was forced to leave because of illness. He returned to Johns Hopkins and received his M.D. degree in June, 1918. Following graduation he was given a scholarship in the Trudeau School of Tuberculosis and later joined the staff of the Metropolitan Life Insurance Company's Hospital at Mount McGregor, N. Y., where he remained four years as pathologist. The following year he was pathologist at New York State Hospital, Ray Brook, and then became associate resident in medicine at the Albany City Hospital, Albany, N. Y. He moved to Asheville, N. C., and began the private practice of medicine in 1924. He served on the staffs of Asheville Memorial Hospital and Biltmore Hospital.

Dr. Craddock was a member of the Buncombe County Medical Society, Medical Society of the State of North Carolina, Southern and American Medical Associations. He had been a Fellow of the American College of Physicians since 1930.

Dr. Craddock was naturally modest and retiring, but his absolute sincerity and honesty won for him the respect and affection of those who knew him. Because of his professional acumen, keen insight and common-sense application of his knowledge, he was recognized as an outstanding physician and diagnostician of western North Carolina. He will be sorely missed by his colleagues and patients.

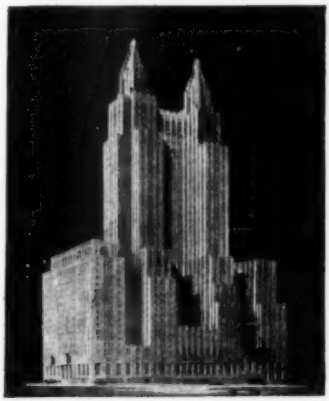
WALTER R. JOHNSON, M.D., F.A.C.P.



A skyline view of the southern tip of Manhattan Island from the East River.

NEW YORK AS A MEDICAL CENTER*

To the average non-New-Yorker, America's largest city is a city of machines, of crowds and indifference. He is appalled by the contrast with his own community, in that here each person apparently goes his own way with little regard for the needs, wants and welfare of others. The friendliness and warmth of his own home town is lacking. But that is the New York which one gets to know only from short and casual observation.



Waldorf-Astoria Hotel
General Headquarters.

The warmth, spirit and heart of the Big City of O. Henry, Mark Hellinger and Damon Runyon can be fully understood only by those who know New York intimately. There is no better objective evidence of our high regard for human life and welfare than in our medical services. Exclusive of federal and state hospitals, there are at present within the boundaries of New York City proper 145 hospitals. Of these, 85 are under voluntary auspices, 14 are maintained by the city, and 46 are proprietary. They have a combined total of 32,071 beds, of which 9,232 are in municipal hospitals, 19,441 in voluntary hospitals, and 3,398 in proprietary institutions.

In THE MASTER PLAN FOR HOSPITALS AND RELATED FACILITIES issued by the Hospital Council of Greater New York, it was reported that in 1946 there were four hospitals with 882 beds for communicable diseases, all under municipal auspices. An additional 76 beds were available as an assigned service of a general hospital, and 35 general hospitals had 105 beds classified as isolation facilities. The number of days of hospital care for communicable diseases has dropped from 244,686 in 1940 to 116,856 in 1945.

In 1946, there was a total of 20 hospitals providing services for the care of patients with tuberculosis, with 16 of the hospitals with 4,495 beds within New York City. The number of new cases of tuberculosis in New York City dropped from 9,466, or a rate of 129.8, in 1935, to 7,062, or a rate of 91.4, in 1945. Deaths from tuberculosis dropped from 4,371, or a rate of 59.9, to 2,513, or a rate of 45.4, during the period, and total patient-days for care of the disease dropped from 1,972,698 to 1,803,549.

* This article was contributed by the Committee on Publicity, 30th Annual Session.
Illustrations for this article were generously provided by the New York Convention and Visitors' Bureau.

Most of the beds for the care of patients with mental disease are provided by the State. Eleven hospitals, with a bed capacity of 11,895 beds, are located within New York City. One of these, with 89 beds, is part of a voluntary hospital, and two municipal hospitals, with 705 beds, are operated in connection with general hospitals. A total of 42 hospitals, with 39,819 beds, are available to residents of New York City.

Top Left: Polhemus Memorial Clinic of Long Island College of Medicine, Brooklyn.
Top Right: Queens General Hospital, Jamaica—a newer city hospital.
Center Right: Kings County Hospital, Brooklyn—one of New York's largest.
Bottom Left: Montefiore Hospital.
Bottom Right: New York University College of Medicine.

The first city in America to establish a convalescent home, New York has 37 such homes or institutions, with 2,379 beds, all under voluntary auspices, which provide facilities for the care of convalescent patients. Only 10 of the homes, with 502 beds, are in New York City, and only one, with 60 beds, is a branch of a general hospital.

New York was also the first city to have a specialized hospital for chronic disease. Established in 1884 as a tribute to the 100th birthday of Sir Moses Montefiore, the revered British philanthropist, the original Montefiore Home provided 26 beds for the care of chronic invalids. The Goldwater Memorial Hospital for Chronic Disease, a 1500 bed institution erected on Welfare Island in 1939, is the first municipal hospital of its type. New York has 13 institutions, with 4,701 beds, which are devoted to patients with long-term illnesses. Twelve of the institutions, with 3,201 beds, are under voluntary auspices; the other is Goldwater. In addition, about half of the facilities provided in homes for the aged and in City Home and Farm Colony, and 1,770 beds in private nursing homes are used for this type of care. However, a large percentage of the beds in general hospitals are now occupied by patients who would use facilities for the care of long-term illnesses if they were available. Some 22.5 per cent of the general-care beds in municipal hospitals are occupied by such patients. The New York City Department of Hospitals, however, has recently started a home-care program patterned after the successful demonstration of Montefiore Hospital, which, it is hoped, will reduce the number of such patients now occupying general-care beds.

In 1947, 914,928 patients were treated in New York City hospitals, 518,116 in voluntary hospitals, 266,994 in municipal hospitals and 129,818 in proprietary hospitals. They spent a total of 12,441,036 patient days, 6,034,266 of which were in voluntary hospitals, 5,531,232 of which were in municipal hospitals, and 875,538 of which were in proprietary hospitals. The average length of stay of general medical-care patients was 12.4 days. Patients in voluntary hospitals averaged 10.7 days as compared with 15.6 days in municipal hospitals. In addition, 6,151,180 visits were made to out-patient services, 3,428,157 of which were to the out-patient departments of voluntary hospitals. Our ambulances made over 300,000 calls last year. During the war period, ambulance attendants were used in the ambulance service rather than physicians, but within the last three months internes have started to ride the ambulances again.

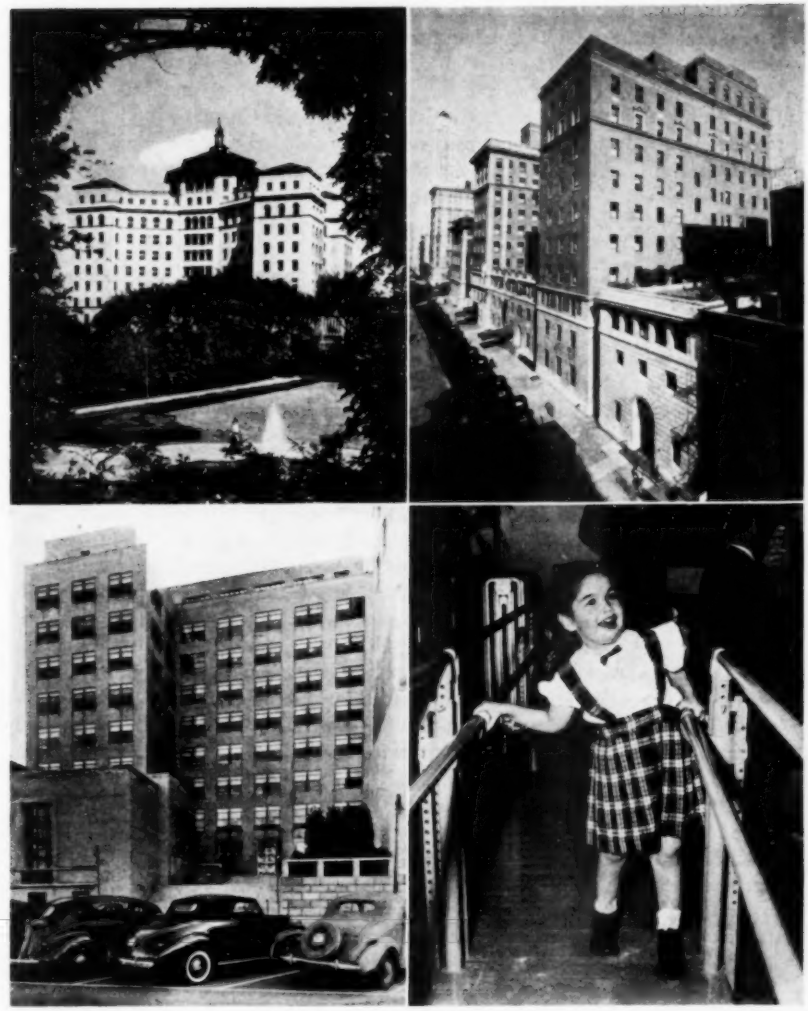
Of the 28,584 beds in 113 general-care hospitals in 1946, 4,364, or 15.3 per cent, were one-person rooms; 3,586, or 12.6 per cent, were in two-bed rooms; 1,497, or 5.2 per cent, were in three-bed rooms; 2,612, or 9.1 per cent, were in four-bed rooms; and 16,525, or 57.8 per cent, were in rooms with more than four beds. Of the 18,761 beds in voluntary hospitals, 20 per cent were one-bed rooms and 47.1 per cent were in rooms with more than 4 beds. Only 3.4 per cent of 8,096 beds in municipal hospitals were in one-person rooms as compared with 88.6 per cent in rooms with more than four

beds. In the proprietary hospitals, 18.9 per cent of the beds were in one-person rooms, and 29.8 per cent in wards of more than four beds.

There is a marked similarity between the voluntary and proprietary hospitals in the percentages of their respective bed complements allocated to general medicine and surgery, and those unassigned. A relatively small proportion of the total complement of beds is assigned to the medical and surgical specialties. In 1946, sixteen general hospitals reported a total of 720 beds allocated to orthopedic patients. Of the 1,432 beds assigned to eye, ear, nose and throat patients, 640 were in six hospitals devoted solely to these specialties.

New York Academy of Medicine.

New York has approximately 18,000 registered physicians, more than the States of Alabama, Arizona, Arkansas, Colorado, Delaware, Idaho, Maine, Montana, Nevada, New Hampshire, New Mexico, North Dakota, Rhode Island, South Dakota, Utah, Vermont, Wyoming, Mississippi, Nebraska, Oregon and South Carolina, combined. Many of these physicians are graduates of our five medical schools: The Columbia University College of Physicians and Surgeons, 622 West 168th Street; Cornell University Medical College, York Avenue at 69th; New York University College of Medicine, 477 First Avenue; Long Island College of Medicine, 350 Henry Street,



Top Left: Hospital of the New York Medical College Flower and Fifth Avenue Hospitals.
Top Right: Lenox Hill Hospital.
Bottom Left: College buildings of the New York Medical College Flower and Fifth Avenue Hospitals.
Bottom Right: Child in Cerebral Palsy Clinic, Lenox Hill Hospital.

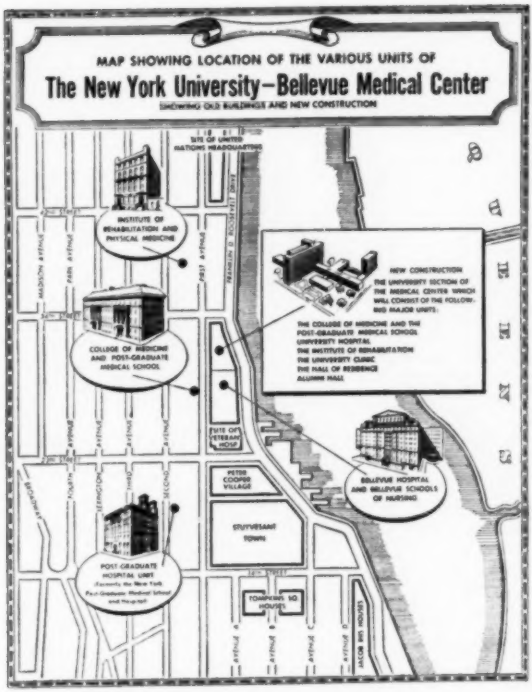
Brooklyn; and the New York Medical College, 105th Street and Fifth Avenue. The oldest of the schools is Columbia University College of Physicians and Surgeons, which had its origin in a school of medicine established in 1767 in connection with King's College. We have two great medical centers in the Columbia-Presbyterian Medical Center and the Cornell Medical Center, and are now witnessing the development of a third, The New York University-Bellevue Medical Center. Announcement has recently been made of the merger of New York Post-Graduate Medical School with New York University.

Center of professional medical activities in New York is the New York Academy of Medicine, which observed its centennial last year. Located at 2 East 103rd Street, the Academy of Medicine is headquarters for many local and national medical organizations. Its medical library, the second largest collection of medical literature in the United States, was recently presented with what has been termed by authorities "the world's first scientific document." It is the Edwin Smith Papyrus, a treatise written by an Egyption physician 4,600 years ago, in which he deals with clinical observation, diagnosis, prognosis and treatment.

New York's interest and leadership in providing medical services dates back to the time when it, too, was a small village. In 1714, when New York was a city of but 8,000 persons, six members of the Common Council met to consider the establishment of a city institution. The institution, which was known as The Publick Workhouse and House of Correction, was built in 1736 on the site of the present City Hall, and was one room measuring 23 by 25 feet, with six beds. To accommodate the ever-increasing numbers of the needy, new buildings were erected, and as the hospital section of the workhouse had become its largest department, it was incorporated as Bellevue Hospital in 1811. By 1848, Bellevue Hospital had become an important teaching institution, and in 1861 a medical school was opened in conjunction with the hospital. This school was combined in 1898 with the New York University College of Medicine which had been started in 1841.

The second oldest general hospital in the nation (the Pennsylvania Hospital was established in Philadelphia in 1751) is New York Hospital, now a part of the Cornell Medical Center. Incorporated in 1771 by the Society of the Hospital of the City of New York, New York Hospital was built in 1775. According to E. H. L. Corwin in his "The American Hospital," "Its inception was due to the efforts of Drs. Samuel Bard and John Jones who thought hospitals afforded the best and only means of properly instructing pupils in the practice of medicine."

That Dr. Bard's concept is widely followed today is shown by the fact that more than 10 per cent of all the internes in this country are receiving training in New York City hospitals. In 1946, New York City had 145 general-care hospitals, with 32,071 beds. Not including Memorial Hospital, which is considered a specialized cancer hospital, 37 of these hospitals,



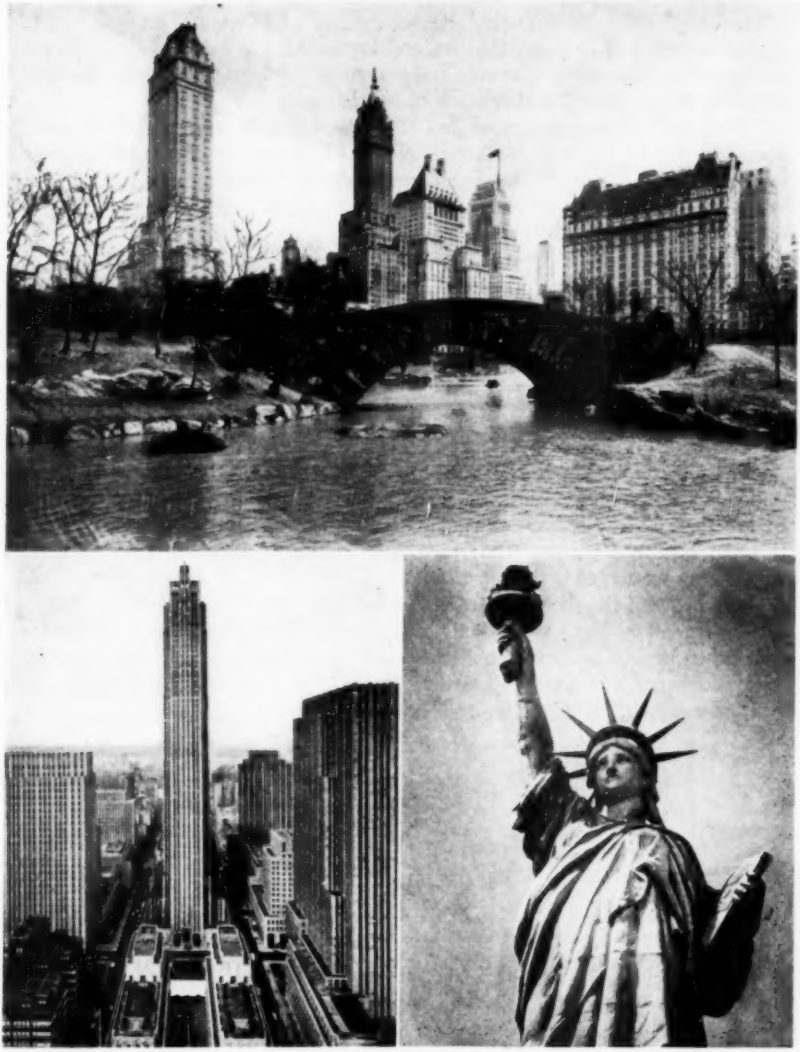
with a total of 24,040 beds, are approved for residency training, and 34.5 per cent of our hospitals are approved for residency training in both medicine and surgery.

Although many hospitals were built before 1860, the greatest growth was following the Civil War. During this period, there was a decided change in public attitude toward hospitals, and they were no longer regarded as institutions for the poor, but were patronized by patients who were able to pay for services. Organized under the auspices of Archbishop Hughes in 1849 by The Sisters of Charity of St. Vincent, St. Vincent's Hospital, the first denominational hospital in the city, was also the first to provide private rooms for private patients.

These are but a few of our many old and new medical institutions and services.

Since the American College of Physicians last met here ten years ago, there have been many changes in our city. New and great medical services and institutions, such as The Public Health Research Institute of the City of New York, Inc., the Sloan-Kettering Institute of Cancer Research, the Montefiore and Department of Hospitals home-care programs, the United

Top: The Columbia-Presbyterian Medical Center.
Bottom: The New York Hospital-Cornell Medical Center.



Top: Situated in the heart of the city and surrounded by skyscrapers is beautiful Central Park.
Bottom Left: Towering Rockefeller Center.
Bottom Right: Statue of Liberty.

Medical Service and Health Insurance Plan of New York, and the Hospital Council of Greater New York, have been started. We stand on our record of medical services to prove that we are not a cold, cynical metropolis, but a community which, despite its size and complexity, places the highest possible premium on the health and welfare of its citizens.

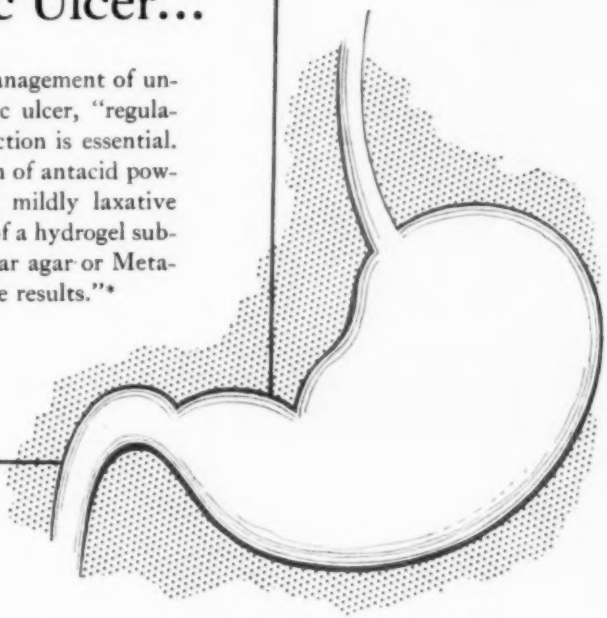
That warmth and understanding is shown not only in our medical services, but also in our many other activities which are of particular interest to our visitors. The general headquarters of the 30th Annual Session, the Waldorf-Astoria, is the center of many activities. Stretching from the towering Empire State Building at 34th Street up to Central Park at 59th Street, is famous Fifth Avenue, style and shopping center of the nation. On up Fifth Avenue, at the corner of 82nd Street, is the Metropolitan Museum of Art, and a few blocks beyond, at the corner of 104th Street, just past the Academy of Medicine, is the Museum of the City of New York. Across the park, on Central Park West and 79th Street, is the American Museum of Natural History and Hayden Planetarium. The especially fascinating Museum of Modern Art, at 11 West 53rd Street, is just a few blocks from the headquarters.

At 50th Street on the Avenue of the America's, which New Yorkers still call Sixth Avenue, is Rockefeller Center and Radio City, home of many of the nation's radio and television broadcasts. Visitors may also be interested in the Museum of Science and Industry, which is located here. Moving on westward is the most famous of all New York sights—Broadway and the heart of the theatre district.

To list all of New York's fabulous attractions is impossible. Information on them will be available at the headquarters; or you can just ask any New Yorker. The chances are that you will find he, too, came originally from Kansas, Iowa, Alabama or Texas.

Bowel Regulation in Peptic Ulcer...

In the medical management of uncomplicated peptic ulcer, "regulation of bowel function is essential. . . . A combination of antacid powders . . . having mildly laxative effects or the use of a hydrogel substance, such as agar agar or Metamucil, will produce results."*



By furnishing a water-retaining, gelatinous residue in the large bowel, Metamucil acts gently without irritation to promote smooth, normal evacuation.

METAMUCIL®

is the highly refined mucilloid of Plantago ovata (50%), a seed of the psyllium group, combined with dextrose (50%) as a dispersing agent.

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY

SEARLE RESEARCH IN THE SERVICE OF MEDICINE

*Gerendasy, J.: Modern Treatment of Peptic Ulcer, J. M. Soc. New Jersey *43*:84 (March) 1946.

STERILE HIGH TITER

GROUP SERA

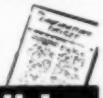
For ACCURATE CLASSIFICATION

Improper classification, due to weak reacting testing sera or failure to differentiate A_1 from A_2 bloods may cause serious trouble—even fatalities.

Our Grouping Sera are certified for HIGH TITER. Exclusively prepared under the personal supervision of Dr. R. B. H. Gradwohl for safe, efficient, accurate laboratory technique. We invite your inquiries.

Our sera are manufactured under Government License No. 160, N.I.H. These sera are Anti-A, Anti-B, and Absorbed Anti-A. Absorbed Anti-A serum is to differentiate between A_1 and A_2 bloods. Anti-M and Anti-N sera are used for blood spots and paternity work. Our Anti-Rh serum is manufactured by the Blood Bank of Dade County and must be used with a viewing box.

Write for a sample copy of The Gradwohl Laboratory Digest full of helpful hints on improved laboratory technique.



GRADWOHL LABORATORIES

R. B. H. Gradwohl, M. D., Director

3514 Lucas Av. St. Louis, Mo.

WANTED

Copies of

ANNALS OF INTERNAL MEDICINE

Good used copies of the *following* issues are now needed.

$1.25 each for

Vol. II, No. 5—November, 1928
Vol. XXV, No. 1—July, 1946

$1.00 each for

Vol. VII, No. 3—September, 1933

75¢ each for

Vol. XXIV, No. 1—January, 1946
Vol. XXIV, No. 4—April, 1946
Vol. XXV, No. 2—August, 1946
Vol. XXVII, No. 1—July, 1947
Vol. XXVIII, No. 1—January, 1948
Vol. XXIX, No. 1—July, 1948
Vol. XXIX, No. 3—September, 1948

Address journals to:

E. R. LOVELAND, Executive Secretary
4200 Pine Street Philadelphia 4, Pa.

THE AMERICAN COLLEGE OF PHYSICIANS

OFFICERS, 1948–49

President ..... WALTER W PALMER, New York, N. Y.
President-Elect ..... REGINALD FITZ, Boston, Mass.
First Vice President ..... WILLIAM S. MIDDLETON, Madison, Wis.
Second Vice President ..... MAURICE C. PINCOFFS, Baltimore, Md.
Third Vice President ..... CHARLES E. WATTS, Seattle, Wash.
Treasurer ..... WILLIAM D. STROUD, Philadelphia, Pa.
Secretary-General ..... GEORGE MORRIS PIERSOL, Philadelphia, Pa.
Executive Secretary ..... E. R. LOVELAND, Philadelphia, Pa.

REGENTS

Term Expiring 1949

ERNEST E. IRONS, Chicago, Ill.
WILLIAM S. MCCANN, Rochester, N. Y.
T. GRIER MILLER, Philadelphia, Pa.
CHARLES F. MOFFATT, Montreal, Que., Can.
CHARLES F. TENNEY, New York, N. Y.

Term Expiring 1950

DAVID P. BARR, New York, N. Y.
ALEX. M. BURGESS, Providence, R. I.
ERNEST H. FALCONER, San Francisco, Calif.
CYRUS C. STURGIS, Ann Arbor, Mich.
A. B. BROWER, Dayton, Ohio

Term Expiring 1951

HUGH J. MORGAN, Nashville, Tenn.
WALTER B. MARTIN, Norfolk, Va.
LEROY H. SLOAN, Chicago, Ill.
GEORGE F. STRONG, Vancouver, B. C., Can.
MARION A. BLANKENHORN, Cincinnati, Ohio

Ex Officio

WALTER L. PALMER, Chicago, Ill.

POSTGRADUATE COURSES

Offered by the

AMERICAN COLLEGE OF PHYSICIANS

January through June, 1949

No. 1—MEDICAL ASPECTS OF NUCLEAR ENERGY; U. S. Army Medical Center, Washington, D. C.; 7 days, January 24–February 1. Fees waived for medical officers of U. S. Army, Navy and Air Force, active and reserve, Public Health Service and Veterans Administration. Others: $40.00, A. C. P. Members; $80.00, Non-members. Under auspices of the Armed Forces Special Weapons Project and the American College of Physicians. Lectures, demonstrations and motion pictures on applications and significance of atomic energy to physicians. Lt. Col. Karl Houghton, (MC), USA, *Director*.

No. 2—GASTRO-ENTEROLOGY; The Stanford University School of Medicine and The University of California Medical School, San Francisco, Calif.; 1 week, February 7–12; $30.00, A. C. P. Members; $60.00, Non-members. A survey of recent and significant developments in this field, with emphasis on physiology, biochemistry and pathology. Dwight L. Wilbur, M.D., F.A.C.P., and T. L. Althausen, M.D., F.A.C.P., *Directors*.

No. 3—CLINICAL MEDICINE FROM THE HEMATOLOGIC VIEWPOINT; Ohio State University College of Medicine, Columbus, Ohio; 1 week, February 14–19; $30.00, A. C. P. Members; $60.00, Non-members. Newer techniques for securing hematologic data; interpretation of data for clinical management and specific therapy. Charles A. Doan, M.D., F.A.C.P., *Director*.

No. 4—INTERNAL MEDICINE; Massachusetts General Hospital, Boston, Mass.; 2 weeks, March 7–19; $60.00, A. C. P. Members; $120.00, Non-members. Exercises in application of theory to practice. General topics: endocrinology, cancer, cardiovascular diseases, nutritional problems of gastro-intestinal diseases, preventive aspects of clinical medicine, rheumatoid arthritis. James H. Means, M.D., F.A.C.P., *Director*.

No. 5—ELECTROCARDIOGRAPHY; Massachusetts General Hospital, Boston, Mass.; 1 week, April 25–30; $60.00, A. C. P. Members; $120.00, Non-members. Basic principles of electrocardiography; interpretation based on current knowledge of the physiology of heart muscle. Conger Williams, M.D., *Director*.

No. 6—DISEASES DUE TO ALLERGIC AND IMMUNE MECHANISMS; Haddon Hall Hotel, Atlantic City, N. J.; 4 days, April 28–May 1; $30.00, A. C. P. Members; $60.00, Non-members. Immunology, pharmacology, physiology, and clinical phases of diseases caused by immune mechanisms. Given at Atlantic City for convenience of physicians having meetings there at the time. Leo H. Criep, M.D., Associate Professor of Medicine, University of Pittsburgh, *Director*.

No. 7—CARDIOVASCULAR DISEASE; Philadelphia Institutions; 1 week, May 2–7; $30.00, A. C. P. Members; $60.00, Non-members. Lectures, panel discussions and clinical demonstrations; recent advances in knowledge, diagnosis and treatment. William G. Lennan, Jr., M.D., F.A.C.P., Professor of Medicine, Woman's Medical College of Pennsylvania, *Director*.

No. 8—PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE; University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; 1 week, May 9–14; $30.00, A. C. P. Members; $60.00, Non-members. Why symptoms occur; how drugs act; why and how clinical physiological tests are used in diagnosis. Julius H. Comroe, Jr., M.D., F.A.C.P., *Director*.

No. 9—ENDOCRINOLOGY; Tufts College Medical School, Boston, Mass.; 1 week, June 13–18; $30.00, A. C. P. Members; $60.00, Non-members. Emphasis on fundamental sciences contributing to endocrinology and recent advances in clinical endocrinology. Edwin B. Astwood, M.D., F.A.C.P., *Director;* E. W. Dempsey, M.D., and Roy O. Greep, M.D., *Associate Directors*.

FOR DETAILED INFORMATION AND REGISTRATION BLANKS, address The Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

Place of Publication—Prince and Lemon Sts., Lancaster, Pa.

Editorial Office—University Hospital, Baltimore 1, Md.

Executive Office—4200 Pine Street, Philadelphia 4, Pa.

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. DOE, J. E.: What I know about it, Jr. Am. Med. Assoc., 1931, xcvi, 2006-2008.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

REPRINTS. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

REVIEWS. The ANNALS will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the Editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

SUBSCRIPTION. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscriptions may be by volume or by year. Volumes will consist of approximately 1,300 pages. Subscription price per annum, net postpaid: $10.00, United States, Canada, Mexico, Cuba, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.25. Members of the American College of Physicians receive the ANNALS OF INTERNAL MEDICINE in connection with the payment of annual membership dues, of which nine dollars is for a year's subscription to the publication. Checks should be drawn to the order of W. D. STROUD, M.D., Treasurer, and remitted through the Publication Office or the Executive Secretary's Office.

BUSINESS CORRESPONDENCE. All correspondence relating to business matters, advertising, subscriptions to the ANNALS, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Publication Office or to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

ASSOCIATE EDITORS

David P. Barr ..... New York
Robert A. Cooke ..... New York
James H. Means ..... Boston
O. H. Perry Pepper ..... Philadelphia
James J. Waring ..... Denver

ASSISTANT EDITOR

Paul W. Clough ..... Baltimore

EDITOR
MAURICE C. PINCOFFS, M.D.
University Hospital
Baltimore 1, Md.

EXECUTIVE SECRETARY
EDWARD R. LOVELAND
American College of Physicians
4200 Pine Street, Philadelphia 4, Pa.

LANCASTER PRESS, INC., LANCASTER, PA.